Feasibility and Optimization of a P300-based Brain Computer Interface in Individuals with Amyotrophic Lateral Sclerosis

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DEDICATIONS

This thesis is dedicated to those struggling in the never ending battle against Amyotrophic Lateral Sclerosis. You have provided me with a new lease on life and a passion to succeed. Realize that you are changing the lives of everyone who meets you. Without your hours of tireless participation this research would not have been possible, and for that selfless dedication I thank you.

To WJG, KAM, and MJS, may you rest in peace and may the white of winter continue to fall down upon you bitter, bright, and briskly. You are missed and will never be forgotten.

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ABSTRACT

Feasibility and Optimization of a P300-based Brain Computer Interface in Individuals with Amyotrophic Lateral Sclerosis
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Amyotrophic Lateral Sclerosis is a neuromuscular disease characterized by progressive weakness resulting in a state of profound disability including the loss of functional speech. The rise of new technologies allows people living with ALS and other individuals with severe motor disabilities to communicate using alternate methods. One alternative communication method is an Electroencephalographic (EEG) based brain-computer interface (BCI), which uses a cap embedded with electrodes to read EEG signals. In particular, the P300, a naïve response to stimuli, is used. Through a P300 Speller paradigm, the EEG-based BCI allows individuals with severe disabilities to communicate using a computer even when conventional devices that require mechanical manipulation have failed.

An electrode test system was designed to determine whether the commercial electrode cap was functioning correctly. Direct input from a function generator was provided to 4 electrodes at a time and the resulting signal was measured using a DATAQ acquisition box and signal acquisition software. A generated sine was seen in each electrode with a signal loss of 5-6%. The electrodes were able to adjust to and reflect changes in input amplitude and frequency, demonstrating adequacy in signal acquisition.

Four able-bodied and eight individuals with ALS from the Philadelphia community participated in the P300 Speller trials under informed consent to determine the feasibility of using the BCI in an ALS population. The EEG was recorded with 8 electrodes using an electrode cap. All aspects of data collection were controlled by the BCI2000 system. Users were asked to participate in a copy-spelling session in which they attended to a specified target letter appearing in a letter

matrix. All controls and 6 out of 8 individuals with ALS were considered to be responders (spelling accuracy over 75%). Spelling ability is not correlated to the ALS Functional Rating Scale (ALSFRS), age, or gender. This indicates that individuals who are extremely disabled are able to accurately use a BCI.

There are differences in the P300 signal between healthy controls and individuals with ALS. The latency of the peak amplitude of the P300 signal is significantly ($p=0.020$) later in healthy controls compared to individuals with ALS. The peak amplitude of the P300 signal is not significantly different in healthy controls compared to individuals with ALS. In 3 out of 4 healthy controls, activity can be visualized across all 8 electrodes in the cap whereas in 7 out of 8 individuals with ALS, activity can be visualized primarily in channels 1-4. Changes in latency and signal movement through the electrodes may indicate differences in the electrical wiring in the brain. However, these changes do not affect the ability of an individual to use the BCI and do not influence the amplitude of the signal.

The ground and reference electrode locations were changed to determine the flexibility of the BCI and to optimize electrode placement. Examined healthy controls and individuals with ALS were considered responders at each electrode location. The ideal location and number of flashing sequences varies between individuals, however, the ability to move the electrodes without detriment demonstrates that the system can be manipulated to improve comfort and overall satisfaction with the BCI.

BCIs can be used by individuals with a debilitating disease such as ALS to communicate with the external world and control their environment. The BCI system and the P300 Speller paradigm are dynamic, flexible, and can be made to work for the majority of individuals with both comfort and ease.

1. PROBLEM STATEMENT

Individuals with Amyotrophic Lateral Sclerosis (ALS) and other neuromuscular disorders often have trouble communicating through traditional output pathways. Brain computer interfaces (BCIs) allow for an alternative method of communication and have been shown to work well in healthy controls. The BCI should be made feasible for an ALS population. Additionally, the system should ensure user comfort and spelling accuracy through optimization of individual system components.

2. SPECIFIC AIMS

1. Design an electrode test system to ensure efficient detection of brain waves.

   The current BCI2000 software and protocol does not include determination of working electrodes before the electrode cap is placed on the subject. A model system will allow testing of the cap to ensure that all electrodes are working properly before the cap is used in an experimental or home setting. The user must be able to continue to wear the cap without detriment while this test is performed.

2. Determine the feasibility of using the P300 Speller paradigm of a BCI for healthy controls and individuals with ALS.

   Healthy controls as well as individuals with ALS will be tested to determine the feasibility of using the P300 Speller as a communication device. The P300 signal is different in all individuals. The goal is to determine whether such differences are truly individual or whether they may be attributed to other factors such as gender, age, or disease progression.

3. Optimize the placement of ground and reference electrodes based on spelling accuracy and subject comfort.

   The ground and reference electrodes will be placed on (1) the left and right mastoid, (2) directly below the left and right ear, and (3) 5 cm below the left and right ear with the goal of maximizing subject comfort and system usability.

3. BACKGROUND AND LITERATURE SURVEY

3.1 Amyotrophic Lateral Sclerosis

ALS is characterized by progressive weakness resulting in a state of profound disability including the loss of functional speech. As the motor neuron system degenerates, ALS often manifests in the form of muscle weakness, muscle atrophy, fasciculations, and multiple combinations of corticospinal tract signs [1]. Symptoms are mainly related to muscle control and there is no sensory involvement, either electrically or clinically [2].

Although ALS is the most common motor neuron disease (MND) among adults [1], it is still considered to be a rare disease. The annual incidence of ALS is 1-2/100,000 people and the prevalence is 5/100,000 population with an estimated 20,000-30,000 present cases in the United States [2]. The most common age of disease onset is between 55 and 75 years of age, with males being 1.5 to 2.0 times more likely to be diagnosed. The majority of individuals with ALS die within five years of diagnosis, but 8-22 percent may survive for a minimum of 10 years [3].

3.1.1 The ALS Functional Rating Scale

The ALS Functional Rating Scale (ALSFRS) is a validated questionnaire which measures physical function in the daily living of individuals with ALS. It is often used in clinical trials as well as clinical practice due to its ease of use and correlation with disease status and disability level. The ALSFRS is presented as a score out of 48, where 48 indicates normal daily living habits and 0 indicates complete dependency [4]. The full questionnaire is presented in Appendix A.

3.1.2 Treatment of Symptoms in ALS

Much of the treatment surrounding ALS involves symptom management and supportive therapies. Speech Language Pathologists are used early in the disease process to teach individuals with ALS and their families how to communicate with minimal effort through nonverbal modalities [3]. An assistive technology professional helps individuals with communication issues to explore the myriad of technological communication devices. The rise of new technologies, including BCIs, allows people living with ALS and other individuals with severe motor disabilities to communicate using alternate methods even after other conventional devices have failed.

3.2 Brain Computer Interfaces

There are nearly two million people in the world affected with disorders such as ALS in which the neuromuscular channels that the brain uses to communicate with and control the external environment are disrupted. Those individuals which are most affected risk losing all voluntary muscle control, including respiration and eye movement. Modern life-support technology can be used to prolong life, yet doing so also prolongs the personal, social, and economic burdens of the disability [5].

3.2.1 Options for Enabling Function for Individuals with Disabling Disorders

There are three main options for enabling function once it has been lost due to a disorder. The first option is to compensate for the loss by using alternate methods to perform the same action. Muscles which perform under voluntary control can be used as substitutes for paralyzed muscles. For example, eye movements may be used to answer questions, give commands, or operate a computer program to synthesize speech. The second option is to proceed around breaks in the

neural pathways which control muscles, such as using electromyographic (EMG) activity from muscles above a lesion to control stimulation of paralyzed muscles and restore movement [5].

The third option for individuals with motor impairments is to provide the brain with a non-muscular channel for communication and control. A direct brain-computer interface (BCI) can be used to convey messages and commands from the brain to the external world. A variety of methods, including Electroencephalography (EEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and optical imaging, may be used to perform such a task.

3.2.2 Definition of a Brain Computer Interface

A BCI is generally defined as a communication system in which messages or commands that an individual sends to the external world do not pass through the normal output pathways of peripheral nerves and muscles. A BCI is considered dependent if it does not use the brain's normal output pathways to carry the message but the activity in these pathways is necessary for the generation of brain activity which does carry the output. Although a dependent BCI does not provide the brain with a new communication channel, it is still useful. An independent BCI does not depend on the brain's normal output pathways in any way. The message is not carried by peripheral nerves and muscles and activities in these pathways are not needed to create brain activity which does carry the message. For individuals who lack all normal output channels, independent BCIs are likely to be the most useful, as they only require signal generation dependent on the intent of the user [5].

A BCI accomplishes the user's intent as would the output in conventional neuromuscular channels. It replaces the nerves and muscles with electrophysiological signals and the movements they produce with hardware and software that translates the signals into action. Since the brain's normal output channels rely on feedback, a successful BCI must provide feedback and

interact with any adaptations the brain may make in response to the feedback. Thus, BCI performance depends on interaction between the brain producing the signals measured by the BCI and the actual BCI that translates the signals to commands [5].

3.2.3 The Parts of a Brain Computer Interface

A BCI, like any communication system, requires input from the user, an output, elements which translate the input into output, and a protocol which defines the onset, offset, and timing of operation [5]. The interactions of these elements are shown in Figure 1.

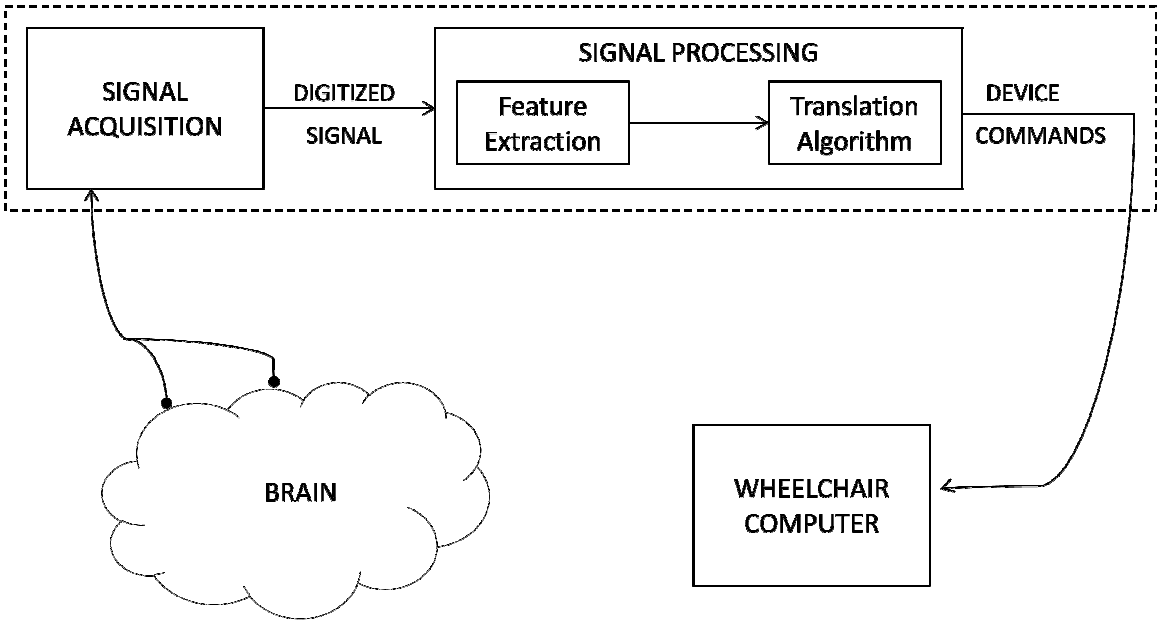

Figure 1: Schematic of the design and operation of a BCI system. Signals from the brain are acquired through electrodes and processed for signal extractions which reflect the intent of the user. These features are then translated into commands which can operate a device. The user must develop and maintain good correlation between intent and the signal features extracted so that device commands are correct and efficient (adapted from [5]).

3.2.3.1 Signal Acquisition

In the signal-acquisition phase of operation, the chosen input is acquired through the recording electrodes. For example, evoked inputs, such as EEG produced by flashing letters, result from stereotyped sensory stimulation. The signal is consequently amplified and digitized [5].

3.2.3.2 Signal Processing

Once the signals are digitized they are subjected to feature extraction procedures such as spatial filtering, voltage amplitude measurements, spectral analyses, and single-neuron separation. The goal is to extract the signal that encodes the user's commands. BCIs may use features in either the time or frequency domain and the use of both may enhance performance. Signal features used to control BCIs today reflect identifiable brain events. The knowledge of the location, size, and function of a particular rhythm or evoked potential dictates how the potential should be recorded and how users may learn to control the potential. A BCI may use signal features which correlate with the user's intent but do not correlate with specific brain events. However, additional efforts must be made to ensure that these signals are not contaminated with non-central nervous system artifacts, such as EMG or electrooculography (EOG) [5].

The first stage of signal processing extracts the specific features of the signal. The next stage is the translation algorithm which translates these features into commands to carry out the intent of the user. Both linear and nonlinear methods may be used to change the signal features into control commands.

The most effective algorithms are those which adapt to the user. When a new user operates the BCI, the algorithm adapts to the individual user's signal features. For example, the algorithm adjusts to the characteristic P300 amplitude of the user. This first level of adaptation will only remain effective if the user's performance is stable. However, variations linked to time of day,

hormones, environment, fatigue, and illness may all cause changes in the signal. Therefore, periodic adjustments are necessary to reduce the impact of spontaneous variation. Ideally, the user's range of feature values will span the available range of command values even over an extended period of time [5].

These levels of adaptation do not take the interaction of the BCI and the brain of the user into account. Thus, the final level of adaptation works with the adaptive abilities of the brain. The brain will modify signal features in order to improve the operation of the BCI. Development of such skills may be rewarded with faster communication abilities in both controls and individuals with muscle diseases [5].

3.2.3.3 The Output Device

Selection of a target can be indicated in a variety of ways including visual and auditory stimuli. Although the actual output of a BCI system is target selection, the output device for current BCIs is a computer. Through a computer output, BCIs can provide cursor movement, communication programs, and prosthesis control [5].

3.2.3.4 The Operating Protocol

A standard protocol guides the operation of each BCI system. It determines how the system is powered on and off, the continuity of communication, the method of message transmission, the sequence and speed of interactions with the user, and the type of feedback provided. Unfortunately, most laboratory BCI systems do not provide the user with on/off or message control [5]. In order to be fully moved out of the laboratory and into the home, protocol adjustments will need to be made so that the user is able to control and use the device independently.

3.2.4 Brain Wave Measurement Techniques

EEG, PET, fMRI, and optical imaging are all control options for BCIs. However, MEG, PET, fMRI, and optical imaging remain technically demanding as well as expensive. In addition, PET, fMRI, and optical imagining rely on blood flow, have long time constants, and are less amendable to rapid communication. Only EEG offers the possibility of a practical BCI, as it has a relatively short time constant, can function in the majority of environments, and requires relatively simple and inexpensive equipment [5].

Although the EEG reflects brain activity, the resolution and reliability of the detectable information is limited by the great number of electrically active neuronal elements, the electrical and spatial geometry of the brain and head, and the variability in trials of brain function. However, scientific studies have shown that the relationships between evoked potentials, their mechanisms of origin, and their relationships with brain function are no longer unknown. In addition, EEG-based communication requires the ability to analyze the EEG in real time. The rapid development of inexpensive computer hardware and software allows for online analyses of a multichannel EEG [5]. The advancements of science and technology have placed scalp-electrode EEG communication in a practical realm.

3.3 The Source of the Electroencephalography Signal [6]

EEG is the difference in voltage between two different electrode locations over a period of time. One electrode is placed on the scalp and at least one additional electrode is placed elsewhere on the body to ensure a voltage difference can be determined.

EEG is produced mainly by cortical postsynaptic potential changes which alter the electrical charge present across the pyramidal cell membrane. These cortical neurons have a membrane potential equal to the difference between the interior cell potential and the extracellular space.

This resting potential changes as a result of extraneous impulses arriving from other neurons on the cell body. These impulses cause electrical current flow along the cell body membranes and dendrites. Such changes can reduce the membrane potential to generate an action potential which may be propagated along the axon. The changing EEG signal is a temporal and spatial summation of thousands of inhibitory and excitatory postsynaptic potentials of the pyramidal cells.

In addition to these postsynaptic potentials there are also intrinsic cellular currents that are mediated by ionic channels producing extracellular potentials with high amplitude and long duration. Most likely, these extracellular potentials also contribute to the signal seen on the EEG monitor. Intrinsic currents are present in neocortical cells which produce a discharge of a cluster of action potentials. This firing in combination with an afterhyperpolarization potential creates an event lasting longer than a general synaptic potential. In addition, this burst firing tends to occur with other neurons in the cell population. These characteristics are important for creating potentials which may be recorded at the level of the scalp. Single action potentials contribute very little or nothing to the recorded EEG.

3.3.1 The Resting Potential of the Neuron

The resting potential of a neuron generally lies between -40 and -80 millivolts (mV) with an average value of -65 mV and is negative on the inside of the cell membrane with respect to the extracellular region. The passive properties of this potential do not require metabolic energy and result from impermeability of the membrane to sodium, potassium, chloride and other ions. Diffusion, along with electrical gradients, helps to drive ions out of the cell for even distribution across the membrane. Active properties of the membrane need metabolic energy to counteract ion leakage across the membrane. The most important active transport is the sodium-potassium pump, which is responsible for transporting sodium out of the cell and bringing potassium into

the cell. Conditions that disrupt metabolism within the brain may reduce the action of this pump, thus reducing the membrane potential and increasing excitability within the neuron.

3.3.2 Postsynaptic Potentials in Nerve Cells

Postsynaptic potentials are due to action potentials from other neurons arriving at a nerve cell through an axon. The impulse in the afferent neuron causes the release of a neurotransmitter substance which diffuses across the synaptic cleft to interact with a specialized receptor. The interaction creates a change in membrane permeability to certain ions and there is a local change in membrane resting potential.

An excitatory postsynaptic potential (EPSP) is a partial reduction in membrane potential. It is transient and most often due to increased permeability of the membrane to sodium and potassium ions. The entry of sodium into the cell results in partial depolarization. On the other hand, an inhibitory postsynaptic potential (IPSP) is caused by the entry of chloride ions into the cell and increases negativity. Even though the cell is relatively negative inside, a high extracellular chloride concentration causes an influx of ions. IPSPs generated at different areas of the cell likely sum to hyperpolarize the cell. The neuronal membrane potential is altered by several mV and may last over 100 milliseconds (ms) as electrical current flows change the membrane potential in the cell body.

3.3.3 Action Potentials

Action potentials arise when the neuronal membrane becomes depolarized above a particular threshold value. The threshold is lowest at the axon hillock, where most depolarization occurs. If the membrane becomes depolarized by at least 10 mV a sequence of events ensues. There is a brief increase in membrane permeability to sodium and potassium ions leading to a quick reversal in membrane potential and subsequent repolarization. The electrical change lasts for about 1 ms

and is approximately 100 mV. This action potential does not penetrate deeply into extracellular space, but a wave of excitation follows throughout the cell membrane to cause an EPSP or IPSP to occur in other neurons.

3.3.4 Summation of Electrical Potentials in the Cortex

The summation of electrical potentials mainly occurs in vertically oriented large pyramidal cells for specific reasons. The dendrites of the pyramidal cells extend throughout the majority of the layers of the cortex, allowing a guide to current flow developed in both deep and superficial layers. The cells are arranged in parallel in vertical columns to facilitate spatial summation. Groups of neurons receive similar inputs and respond with changes in potential that are similar in direction and timing. Only one afferent axon is needed to contact several thousand cortical pyramidal neurons. Finally, each pyramidal cell maintains over 100,000 synapses, allowing input to the cells to be magnified.

The currents created by pyramidal cells are summed in the extracellular space. Although the majority of the current is limited to the cortex, a small amount is able to penetrate to the scalp. Different currents cause different areas of the scalp to be at different potential levels. Even though these differences are usually only between 10 and 100 μV, they can be recorded through two electrodes and define the EEG.

EEG is the result of individual neuronal potential changes. However, micro electrode activity from individual cells does not correlate well with EEG activity due to the large numbers of potentials summed to generate the ongoing EEG. In addition, it is not possible to know whether the EEG event recorded at the scalp is a consequence of an IPSP or EPSP. Although EPSPs and IPSPs produce opposite directions of current flow, if they are located at opposing ends of the vertical pyramidal cell the current seen by a surface electrode will appear to have the same polarity.

3.4 Using Scalp Electrodes to Record the Electrical Potentials [6]

Electrodes on the scalp will mainly record those potentials summed in the cortex. They may, in rare cases, record potentials generated in distant parts of the brain. Electrodes may also record artifacts, or signals produced outside of the brain. The intensity of the electrical source, its distance from the recording electrode, and its spatial orientation along with the electrical resistance and capacitance between the source and the electrode all determine the amplitude of the recorded potential. Therefore, it is important for the potential to occur near the recording electrode; be generated by cortical dipole layers oriented towards the recording electrode at 90 degrees to the scalp surface; be generated in a large tissue area; and rise and fall at a rapid speed.

EEG recorded with scalp electrodes differs from one recorded with electrodes placed on the cortex. Scalp EEG is lower in amplitude and may be distorted in shape. Higher frequencies are generally attenuated more than lower ones and very fast or brief potential changes may not be seen in scalp recordings. Scalp EEG amplitude may decrease as a result of the increase in electrical impedance between the source and recording electrodes (such as a thick skull which would reduce current flow) or a decrease in the impedance at different stages in the path of the current before it reaches the recording electrode. However, scalp EEG is preferable in a disabled population due to complications seen in surgical placement of electrodes on the cortex.

3.4.1 Scalp Electrode Placement

The International 10-20 system provides uniform coverage of the scalp [7]. Distances between bony parts of the head (the inion, nasion, and preauricular point) are used to create a system of lines that run across the head. These lines intersect at intervals of 10 or intervals of 20% of their total length and electrodes are placed at these intersections. Recording electrodes are identified with an abbreviation indicating the underlying region: prefrontal (Fp), frontal (F), central (C), parietal (P), occipital (O), and auricular (A). The letter z indicates midline sagittal placement,

odd numbers indicate lateral placement on the left, and even number indicate lateral placement on the right. Numbers increase with increasing distance from the anterior posterior midline of the head.

3.4.2 Electrode Placement for the P300

The electrode placement for obtaining one specific wave, the P300, is a modified version of the International 10-20 system which uses only 8 electrodes. The electrodes are placed in locations (1) F_z, (2) C_z, (3) P_3, (4) P_z, (5) P_4, (6) PO_7, (7) O_z, and (8) PO_8. These positions are highlighted in blue as shown in Figure 2. Further explanation of the P300 is given in Section 3.8.

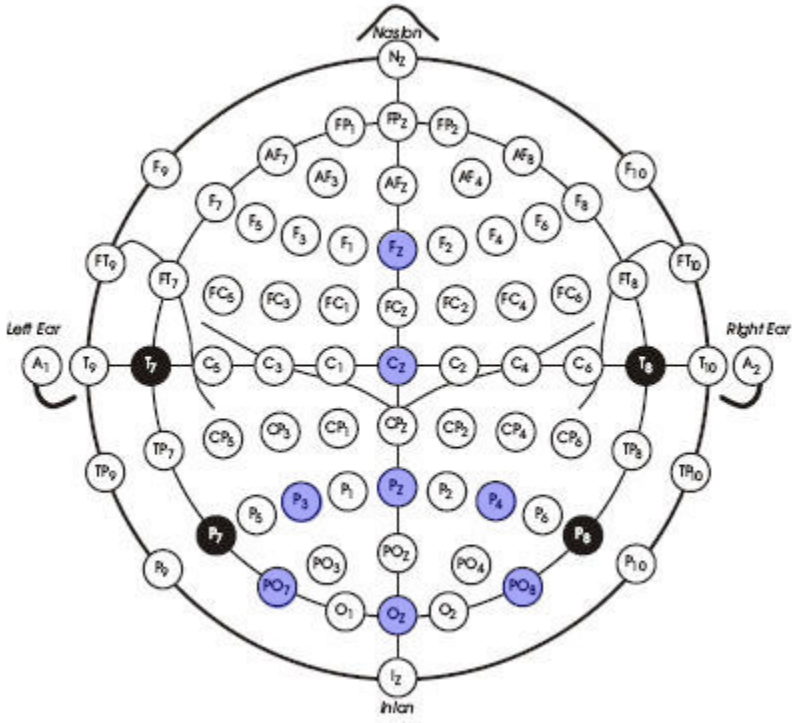

Figure 2: Modified International 10-20 system used for electrode placement when obtaining an EEG in preparation for use of the P300.

3.4.3 Metal Disc Electrodes for Scalp EEG

Metal disc or cup electrodes generally have a diameter between 4 and 10 millimeters (mm). Smaller or larger electrodes result in unstable mechanical and electrical contact with the scalp. Discs should be made of a material which does not interfere with scalp electrolytes, such as gold, silver chloride, tin, or platinum. Insulated wire is attached to each electrode for easy identification of wires and corresponding electrodes. If the wires are attached to one another in the form of a stranded cable, mechanical and electrical problems may be reduced.

Alternative current impedance should lie between 100 and 5000 ohms in diagnostic testing and should be measured before every EEG recording session. Extremely low impedance is not desirable because it acts as a shunt and effectively short circuits the potential differences in EEG. High impedance is not desirable because connecting an electrode of low impedance to one of high impedance creates an imbalance that favors the recording of interference at 60 Hz.

By the time the signal reaches the electrode on the scalp, it has been modified significantly through three main avenues. First, there are multiple tissues which lie between the signal generation in the cortex and the recording electrodes. Each tissue has unique electrical conductive properties which will alter the signal. Second, the signal may not be directed at the recording electrodes. Thus, the orientation may not be direct. Finally, the recording electrode and the scalp-electrode interface have unique conductive properties which may alter the signal. Examples of this include the size of the electrodes, the electrical properties of the materials used, and the impedance resulting at the electrode-scalp junction.

3.5 Parts and Functions of a Digital EEG Instrument [6]

A digital EEG system is simply analog EEG combined with an analog to digital converter to display EEG on a personal computer. Although digital EEG lacks visual clarity of the waveform

there are many useful tools for analysis include montage, filter, and gain selection. Storage space and record retrieval time are also reduced.

3.5.1 Digital Calibration

Calibration for digital EEG instruments can be performed through the use of an external signal generator. A sine wave with a frequency ranging between 0 and 70 Hz should be used. Refer to Section 5 for the design of an electrode test system that may be used while the individual is wearing an electrode cap.

3.5.2 EEG Amplifiers

EEG amplifiers are used to perform differential discrimination as well as amplification. Discrimination refers to the ability of the amplifier to determine a difference in electrical potential between two electrodes while using common mode rejection. Thus, only the difference between the incoming signals to the electrodes is amplified. This differential discrimination allows the amplifier to remove electrical noise from the signal and eliminate electrical potentials which are not from the brain. Single ended amplifiers do not subtract inputs from one another and instead compare the difference between a single electrical input and an electrical ground.

Impedance is a main concern in signal amplification. Unequal impedance in recording electrodes at two input locations causes electrical potentials with the same amplitude to appear with different amplitudes on the recording. This difference will then be enlarged. The most common cause of an imbalance is loss of contact between the electrode and the scalp. In this case, only the difference between a single electrode and the ground is being displayed. Artifacts also play a role, as discussed in section 3.6.

The amplification step increases the difference in voltage between signal inputs. The biological signal may be increased from millivolts to volts and can be characterized in terms of both

sensitivity and gain. The sensitivity (μV/mm) is defined as the ratio between input voltage and the produced signal deflection. A common value is 7 μV/mm but sensitivity of each channel can be adjusted between 1 μV/mm and 1000 μV/mm. A higher value indicates a lower amplification recording and will make a calibration signal appear smaller. Sensitivity can be measured directly and, therefore, is more often used to describe amplification than gain.

Gain is defined as the ratio of signal voltage at the amplifier output to the applied signal voltage at the input. Standard EEG has a maximum gain of 1 million. Unlike sensitivity, gain is defined such that increases in gain correspond with increasing amplification. Because gain cannot be measured directly it is not useful in a clinical setting.

3.5.3 EEG Filters

Filters can used to exclude certain waveforms and record only those frequencies which are in the most important range (1-30 Hz). Filters receive the input signal after it has been passed through the differential amplifier to a single-ended amplifier. Once the signal passes through the filter, the signal is again amplified by single-ended amplifiers. A low frequency filter (Figure 3a), also known as a high pass filter, reduces the amplitude of slow waves and allows higher frequencies to pass through the amplifier without attenuation. A high frequency filter (Figure 3b), also known as a low pass filter, reduces the amplitude of fast waves and allows lower frequencies to remain while attenuating higher frequencies. High frequency filters must include frequencies faster than those considered important in EEG so that muscle activity may be filtered. A notch filter reduces the amplitude of waves in a particular frequency range to remove interference from electrical lines. In North America, this is set at 60 Hz to filter interference from devices powered by alternating current.

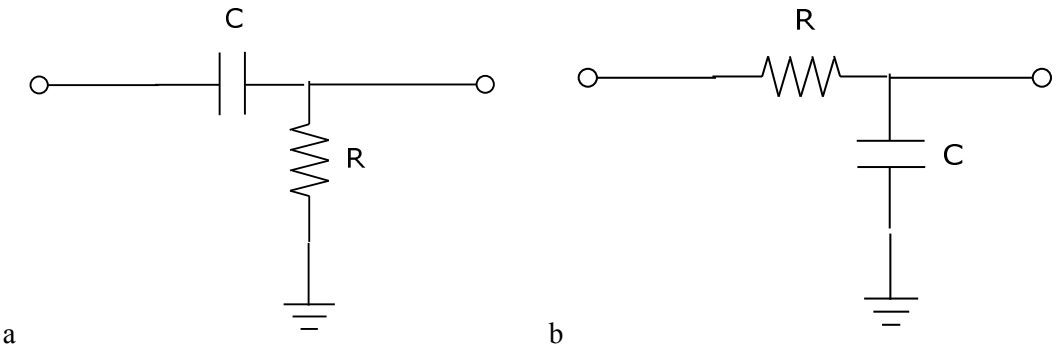

Figure 3: Equivalent electrical circuits for (a) a low frequency filter and (b) a high frequency filter.

Filters distort the time relation between waves of frequencies located close to cutoff frequencies. A phase shift, or phase distortion, occurs as the filters delay or advance these waves in varying time amounts. A low frequency filter advances the peak of a slow waveform whereas a high frequency filter delays the initial deflection of a faster waveform. Such shifts become important in analyzing events which occur in the millisecond range, such as evoked potentials.

3.6 EEG Artifacts [6]

One issue with EEG recordings is the presence of artifacts. Artifacts are potentials seen in EEG that do not originate in the brain. While they may sometimes be recognized by their shape and distribution, they often go unnoticed during the recording session. It is important to realize that potentials which are medium to high amplitude and occur only at a single electrode are normally artifacts. Potentials generated in the cortex demonstrate a distribution across the scalp with a characteristic maximum that gradually drops in voltage with increasing distance. Simultaneous waveforms that are repetitive or irregular and occur in unrelated regions of the head are also usually artifacts. Potentials usually evolve across electrodes and do not jump between locations on opposing sides of the brain.

3.6.1 Artifacts from the Patient

Blinking and other eye movements cause changes which are mainly seen in frontal electrodes. However, these potentials may extend into the central or temporal electrodes. Rapid eye movements will result in jagged artifacts. Traditionally, eye movement artifacts were thought to be due to the movement of the eyeball, as the cornea is about 100 mV positive compared to the retina. However, the movement of this dipole is not needed to produce a blink and simple movements of the lid across the eyeball may result in similar artifacts. In general, it is assumed that activity in the alpha frequency range which is localized to the frontopolar head regions is due to eye movement artifacts. If it becomes difficult to distinguish eye movement from cerebral activity, electrodes may be placed near the eyes and linked to record eye movement.

Muscle activity causes short duration potentials which often occur in either clusters or periodic runs. The spikes may occur as discrete potentials and resemble cerebral spikes or they may occur in rapid bursts and cover the cerebral spikes. Artifacts arising from the scalp and facial muscles are seen mostly in the frontal and temporal electrode recordings. Muscle artifacts can be identified through shape and repetition and can often be reduced or eliminated by requesting that the subject relax, open their mouth, or change position. Some individual electrodes may need to be repositioned. Special EEG patterns are seen in repetitive movements like chewing, blinking, or tremors. Any monorythmic pattern that appears isolated from other background activity should be examined as a possible source of a muscle artifact.

Movements of the head, body, or electrode wires may also cause artifacts. These artifacts are rhythmical and are caused by the force of the blood rushing to the head. They can be recognized by their association with actual movements and can often be eliminated by asking the subject to remain still during recording.

Charges generated in the heart may be picked up in EEG recordings if electrodes are spaced far apart, such as linkages between opposite sides of the head. Such artifacts may appear in all channels if a common reference is used or may only appear in select channels. Smaller artifacts are indicative of the R wave of the electrocardiogram (ECG) whereas larger artifacts may reflect other components. If ECG artifacts are extremely large, they are likely due to the presence of a cardiac pacemaker. Unlike other artifacts, ECG artifacts cannot usually be eliminated and may not be reduced by changing or moving electrodes.

There are two artifacts produced by the skin. The perspiration artifact appears in more than one channel as slow waveforms which are generally longer than 2 seconds in duration. Perspiration causes shifts of the electrical baseline by changing either the impedance of the electrode or the contact between the electrode and the skin. The perspiration artifact can be reduced by cooling the subject and ensuring the scalp is dry through the use of a fan or alcohol.

The second artifact produced by the skin is the sympathetic skin response. It consists of slow wave with duration of 0.5-1 second. This represents an automatic response that is created by sweat glands and skin potentials in response to a sensory stimulus or psychic event. It is more likely to appear as the external temperature increases.

3.6.2 Artifacts from Electrodes and Other Equipment

Artifacts which come from the electrodes and associated wires often appear superimposed on the overall EEG signal and only in one channel. A sudden change in electrical contact will often cause a sharp fall or rise in the EEG. To identify and correct these artifacts, the electrode in question must be checked for electrical and mechanical continuity. The discontinuity may be the result of a broken connection, lack of conductive gel, or faulty wiring.

The most common artifact has a frequency of 60 Hz and is due to electrical interference arising from power lines and equipment. Some amount of this interference is unavoidable in any setting where alternating current is used and it is likely to appear in all channels. It is introduced either electrostatically though unshielded power cables or electromagnetically by cables carrying strong current. Other sources of interference include televisions, radios, ringing telephones, people walking through the room, or the use of an intravenous drip. Since modern EEG machines have high discrimination, all external sources of interference are often rejected.

3.6.3 Artifacts of Concern in Individual with ALS

Many individuals with ALS, especially those further in disease progression, maintain little muscle movement or control. Therefore, muscle and movement artifacts are not of great concern. However, these individuals also often retain the need for external life support and intravenous treatments during system use. Ventilators, cough assist machines, and monitoring devices all contribute environmental interference. In addition, trials with this population are often run in a hospital or home environment. There is frequently extra equipment in the room and health professionals, family members or caregivers passing though the testing area. Since these sources of artifacts and interference cannot be eliminated, one goal of the BCI project is to make the system accurate in the presence of these artifacts such that it may be used in a home or hospital environment as a communication device.

3.7 Types of EEG Brain Computer Interfaces

Current BCI systems fall into 5 categories based on the electrophysiological signals used for system control. The first category uses visual evoked potentials [5] which depend on muscular control of gaze direction. Because many individuals with advanced ALS lose their ability to control eye movement, this is not an adequate choice for the population.

Mu and beta rhythms (Figure 4a) and slow cortical potentials (Figure 4b) require training for BCI use. Mu and beta rhythms are associated with the brain's normal motor output channels [5]. Because such channels may be disrupted in individuals with ALS, this is also not an appropriate choice.

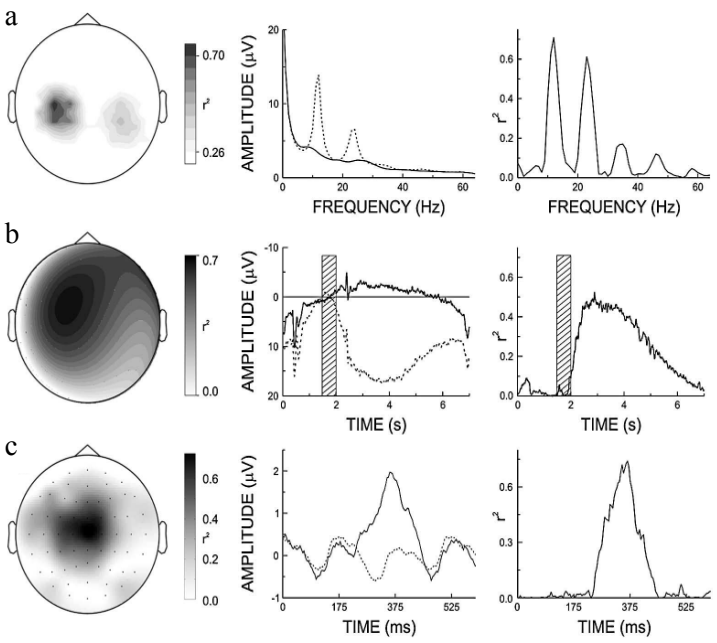

Figure 4: Possible implementations of the BCI. (a) Mu and beta rhythm control of cursor movement. Left: Topographical distribution on the scalp, Center: Voltage spectra for a location, and Right: Corresponding r^2 spectrum for top versus bottom targets. (b) Slow cortical potential control of cursor movement. Left: Topographical distribution on the scalp, Center: Time course for the EEG, and Right: Corresponding r^2 time course. (c) P300 control of a spelling program. Left: Topographical distribution on the scalp, Center: Time course for the EEG, and Right: Corresponding r^2 time course [8].

The P300 wave (Figure 4c) requires no initial user training and is a normal response to the presentation of infrequent stimuli. Use of the P300 evoked potential for BCI use has been successful in ALS populations [9-13]. Therefore, this discussion will focus on systems which use the P300 evoked potential for communication.

3.8 Characteristics of the P300 Wave

The P300 is a robust wave presented in individuals at all ages. It is a typical or naïve response to a desired stimulus. Although the P300 may change or habituate over time, because it requires no initial training, additional translation algorithms may be implemented to maintain a response [5].

3.8.1 P300 Theory

The "oddball" paradigm is often used to elicit the P300. In a single-stimulus trial the target is presented infrequently with no other stimuli. In a two-stimulus trial, an infrequent target is presented in the background of frequent standard stimuli. This is the most common method of stimulation and is known as the oddball paradigm. In a three-stimulus trial, an infrequent target is presented in the background of frequent standard stimuli and infrequent distracter stimuli [14]. These differences are illustrated in Figure 5.

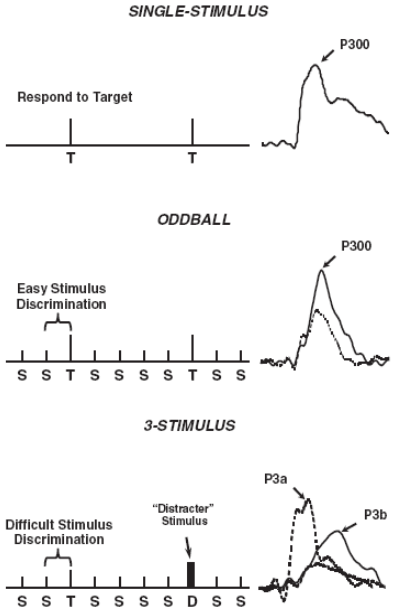

Figure 5: Schematic of the single-stimulus (top), oddball (middle) and three-stimulus (bottom) paradigms [14].

The subject must respond to the stimuli either mentally or physically and must make an effort to respond only to the target stimuli. The target stimuli elicit a potential which increases in amplitude from the frontal to parietal electrodes [14].

The P300 amplitude indexes brain actions when a mental representation of the stimulus environment is updated [15]. This idea stems from a model of orienting response which was derived from the effects of habituation and dishabituation that have been shown to also affect the P300 [14]. After initial sensory processing, the current stimulus entering the brain is compared to the previous oddball stimulus stored in working memory. If there is a change detected in the stimulus attribute, the old stimulus schema is kept and sensory evoked potentials are recorded. However, if a new stimulus is processed, attention mechanisms engage to update the schema. This update of representation within the memory may elicit the P300 [16].

A positive waveform with a maximum amplitude distribution at the central or parietal electrode with relatively short peak latency is called the "P3a". A "novelty P300" is elicited when a subject is presented with non-repeated distracter stimuli such as a dog bark and is associated with redirection of attention monitoring. The novelty P300 is characterized by a maximum amplitude distribution at the frontal and central electrodes, short peak latency, and relatively rapid habituation. Recent studies have shown that the P3a and novelty P300 are in fact the same potential as distinctions between the two cannot be supported [14].

P300 scalp tomography appears to be determined by differences in stimulus and task conditions. Outcomes appear in a fashion which suggests the engagement of overlapping neural activations with a functional distinction between the P3a (seen initially in the frontal and central electrodes) and the emergence of the P3b (seen in the parietal electrode). As shown in Figure 6, initial processing of a stimulus requires early focal attention which determines P3a production. Therefore, frontal lobe engagement is necessary for P3a generation and attention control.

Initiation of frontal lobe activity engages the attention focus which is demanded by task performance. Later memory comparison determines P3b production. The stimulus event does not need to be perceptually novel to generate a signal [14].

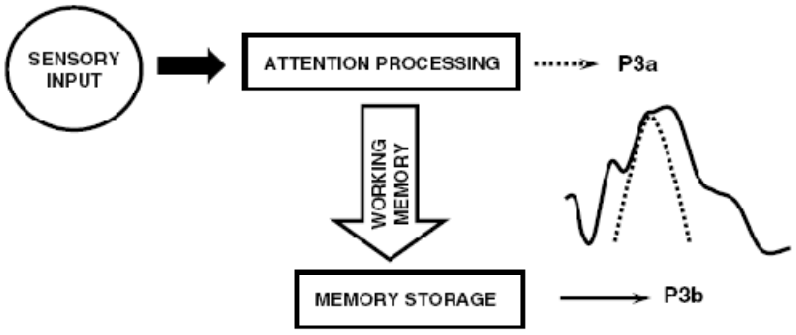

Figure 6: Schematic of cognitive events associated with P300. The P3a is elicited if the stimulus demands focal attention. Working memory engages storage operations to produce a P3b if the subject discriminates the target from other presented stimuli [14].

The neuroelectric events which determine P300 generation arise from the interaction between the frontal lobe and hippocampal/temporal-parietal function. fMRI studies which examine oddball tasks obtain patterns consistent with a frontal-to-temporal and parietal lobe activation pattern. Once the incoming stimulus goes through frontal processing, activity propagates between the cerebral hemispheres and across the corpus callosum [14] to produce the overall waveform of P300 shown in Figure 7.

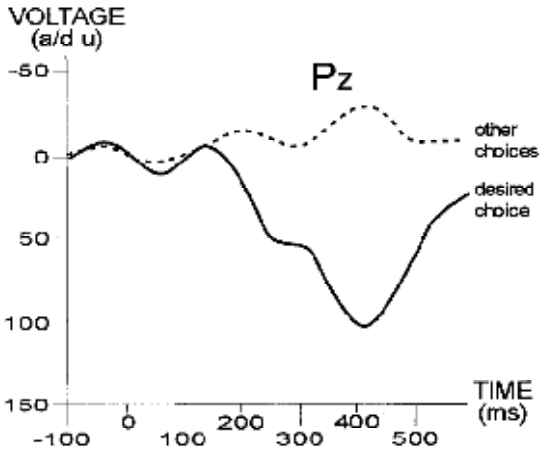

Figure 7: P300 BCI. Only the choice desired by the user evokes a large P300 potential. This is the positive potential which occurs approximately 300 ms after stimulus presentation [5].

3.8.2 Characteristics of the P300

Stimuli of clicks or brief light flashes evoke a characteristic response among individuals when presented at an intensity which is above threshold yet still comfortable. In original experiments presented by Sutton et al., subjects were given two paired stimuli in which each pair had a cueing stimulus and a test stimulus. In the first kind of pairing, the cueing stimulus was followed by a test stimulus which was always a sound or always a light, allowing the subject to be certain of the sensory quality of the test stimulus. In the second kind of pairing, the cueing stimulus was followed by a test stimulus which was either a sound or a light, such that the subject was uncertain of the sensory quality of the stimulus. The waveforms obtained from EEG recordings differ between individuals and stimuli. However, in 36 out of 36 experiments, there is a large positive deflection with peak amplitude at approximately 300 ms [17]. This deflection has been termed the P300 component of the event-related brain potential.

The degree of uncertainty can also be manipulated as shown in Figure 8. Cueing pairs were once again presented, however, in one kind of pair a cue was followed 33% of the time by sound and

66% of the time by light whereas in the second kind of pair the inverse was true. The curves represent the average response for one subject. The top graph shows the effect of sound probabilities on the evoked potentials and the bottom shows the effect of light probabilities on the evoked potentials. Each waveform shows the expected deflection at 300 ms, yet the amplitude is greatest for a lower probability stimulus [17].

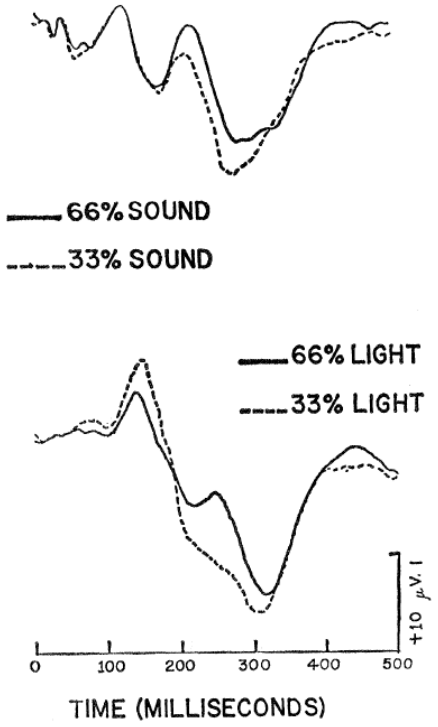

Figure 8: Average waveforms for different probabilities of light and sound with different cueing stimuli [17].

The P300 is operationally defined as a component having a latency longer than 275 ms, positive in polarity at all midline electrodes, having a maximum positive value at parietal and central locations, elicited by stimuli which are task relevant and having an amplitude which is affected by both subjective probability and the task relevance of the stimulus [18]. Operational guidelines recommended by Fabiani et al. detail that the P300 may be identified on the basis of (a) positive

polarity, (b) latency, (c) morphology (a peak must be identifiable), (d) scalp distribution (in general, Pz and Cz > Fz and Pz usually > Cz) and, if possible, (e) established relationships with probability and target effects [19].

P300 scalp distribution is defined as the amplitude change over midline electrodes (Fz, Cz, and Pz according to the International 10-20 system) and typically increases in magnitude from the frontal to parietal electrode locations [20]. The amplitude of the P300 is the difference between the lowest negative point prior to the P300 window (baseline voltage) and the highest positive point within the P300 window [21]. Latency is defined as the time from stimulus onset to the time of maximum positive amplitude within the P300 window [20]. The window is defined as the time range where the average wave form is positive and generally ranges between 220 and 500 ms [21].

To be fully operational, the definition of the P300 must be more than simply reliable. A true definition of the P300 waveform should satisfy three main criteria: (a) feasibility (the definition should be applicable to real data), (b) reliability (if data is obtained under the same condition for the same subject it should reproduce the same results), and (c) validity (the definition should correspond to all characteristics of the P300) [19]. In most cases, reliability is the easiest of the three characteristics to measure accurately and can be examined within a subject for a single session or across multiple sessions by examining the amplitude and latency of the P300.

The amplitude of the P300 varies inversely with the probability of the stimuli and directly with the relevance of eliciting events [21]. Events that require either a response or additional processing elicit larger P300 amplitudes [19]. The subject's ability to accurately discriminate events and place them in appropriate categories is crucial. It is not necessary, however, to report occurrence of a target event through direct communication [21]. P300 signals are present as long

as the subject is able to remain focused on target occurrence and do not require motor or verbal acknowledgement.

Variations in the scalp distribution of the P300 may be related to differential activity of overlapping components or variations in cell populations devoted to the generation of the waveform. The P300 may not arise from a single generator but instead from multiple sources with a variety of orientations [22]. Several neural generators may be needed to carry out what is seen as a single psychological process. The same set of sources may be differentially activated to accommodate the processing changes required by a particular task. This then may lead to slight changes in scalp topography and provide an explanation for the differences seen among individual subjects [19].

Individual differences seen in the P300 latency are correlated to speed of mental function and shorter latencies are related to superior cognitive ability. P300 latency decreases during childhood development and increases with normal aging. Latency also increases as dementia increases [20]. Since individuals with ALS do not tend to have dementia and are within a similar age range, an average profile can be determined.

Stimulus information content, sequence probability structure and the relevance or difficulty of the task are all cognitive factors which affect P300. P300 is sensitive to general and specific arousal effects which contribute to information processing and attention activation. Slow fluctuations in energetic arousal state may affect P300 and can be controlled to reduce individual variation [14].

3.8.3 General Guidelines for the Use of P300 in Published Studies

To account for the differences and possible problems discussed above, general guidelines have been created for the use of P300 waveforms in published studies [19]:

1. Electrodes: Electrodes should be placed at the electrooculographic (EOG), Fz, Cz, and Pz as a minimum for P300.

2. Ocular artifacts: Possible contamination from eye movements should be of a concern to investigators and measures to deal with this problem should be considered[1].

3. Recording epoch: The P300 may be followed by a slow wave which lasts for hundreds of milliseconds. Therefore, the recording epoch should extend at least one second from stimulus onset.

4. Raw records: Due to the use of few subjects, all superaverages and typical waveforms of single subjects should be presented. In addition, at least for some averages, waveforms for each electrode should be presented.

5. Polarity: Polarity convention (as indicated by the '+' and '-' sign) should be reported in all figures as well as in text or legends[2].

6. Amplitude measurement: The methods used to determine the peak amplitude of ERP components must be specified. It is also desirable to use more than one method.

7. Experimental reports: Independent variables should be identified and described. Atypical subjects should not be eliminated without justification. An unusual morphology is not a reason for rejection, unless such morphology results from artifacts which cannot be removed.

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[1] Ocular potentials are known to propagate to scalp electrodes. The EOG electrodes can be used to correct event-related activity in both channels. However, this is not as important for these trials as for locked-in individuals eye movement is not a factor.

[2] Since the publication of these guidelines, it has become standard practice to report the negative deflection of the P300 as a positive deflection when the waveform is presented graphically.

8. Debriefing: All subjects must be debriefed after any experiment. The equipment should be functioning properly, given instructions must be fully understood, and information of the subject's strategies, motivation, and general attitudes toward the experiment should be obtained.

3.8.4 Specific Guidelines for the Use of P300 in Published Studies

After a reliability study involving the P300, a more specific set of guidelines was also developed [19]. These guidelines are to be followed in addition the general guidelines proposed above:

1. Single trials vs. averages: Single trials give more reliable estimates of P300 than averages. This is especially useful in latency estimates. However, single trials are more susceptible to background EEG noise and may provide issues in estimating amplitude. Therefore, both single trials and averages should be analyzed.

2. Filters: Filters may be used to increase the signal-to-noise ratio of the system and improve P300 detection. Appropriate frequency filters may have an upper cutoff point as low as 3 Hz for single trials and 6 Hz for averages. Filters may also be used for scalp distribution (vector filters) and latency analysis. Characteristics of both the P300 signal as well as the noise must be considered.

3. Signal detection algorithms: The best results are obtained with algorithms that use the most information in defining P300. Optimization techniques are also helpful but must be used with caution as they often require a validation procedure.

4. Analysis of scalp distribution: A univariate analysis of variance (ANOVA) model is inappropriate to analyze scalp distribution. To interpret different electrode locations a multivariate model should be used.

5. Multiple analyses: Several measurement procedures should be used in order to strengthen conclusions.

6. Multiple sessions: If subjects are run in multiple sessions to obtain a sufficient number of trials each session should contain all experimental and control conditions. If this is not possible, random experimental designs should be used. Data obtained in different sessions should be analyzed separately and pooled only when similar results are obtained.

3.9 Initial Studies of the P300 in Brain Computer Interfaces

Initial spelling programs were tested by Farwell and Donchin (1988) in which the purpose of the study was to determine whether four mentally intact young adults could use a version of the oddball paradigm to communicate a five letter word to a computer. Ag-AgCl electrodes were placed at the Pz site and referenced to linked mastoids. The Pz location was chosen as this is the site of the largest P300 amplitude in young adults. Electrode impedance remained below 5 kilo-ohms (kΩ) [21].

The first area addressed by the study was to determine whether the P300 can be used as a switch to make a choice. It was determined that the P300 can act as a binary switch as well as allow for the choice of one item out of a number of distinct items (1 letter or word out of 36 letters or words in this design). The P300 can be used for categorization, provided that one of the categories is presented at a lower frequency. The use of short inter-stimulus intervals (shorter than the latency of P300) does not interfere with elicitation of the P300. As such, the P300 may be used to respond to task-relevant events. It is important to note that the use of the P300 as a communication channel is dependent on the signal to noise ratio of the overall system and signal averaging is required. In addition, detection methods vary in their effectiveness and alternative algorithms may be more effective in certain cases [21].

3.9.1 Early Results of P300 in ALS Populations

Sellers et al. examined the use of the P300 Speller as described by Farwell and Donchin [21] in individuals with ALS. 15 individuals with ALS and one with a brainstem stroke were asked to use the P300 Speller in two sessions approximately six weeks apart. Nine of the people were able to reach levels of accuracy greater than 75%. The remaining individuals were unsuccessful using the program (accuracy level < 50%). However, all seven of these users were either locked-in at the time of testing or were only able to communicate with their primary caregiver. Each user's waveforms were unique, as is expected in P300 trials. Individual's waveforms were similar over time, indicating that the P300 response does not habituate and remains stable over a period of weeks [13].

Moving from a laboratory to a home environment introduces additional complications. Ventilators may introduce either electrical or mechanical artifacts as well as movements of the head. These disturbances can manifest as frequency drift. In locked-in individuals there are concerns with perceptual and cognitive abilities. It is not truly known whether the person is attentive, can see the display, or attend to the correct character. In addition, the level of cognitive ability is unknown [13].

3.10 Summary

Individuals with ALS lose the ability to communicate through traditional motor output pathways as the disease progresses. A BCI allows for partial restoration of communication. While there are many methods of obtaining brain signals, EEG can be accurately used to obtain an electrical signal from the brain without the need for invasive surgery. In particular, a P300-based BCI can be used by individuals with severe disabilities to control a computer without additional training. Further research involving individuals with ALS may lead to unique classification methods which could help to improve the system for this population.

4. PROPOSED NEW APPROACH

4.1 Hypothesis

Though spelling ability and characteristics of the P300 waveform (including latency and amplitude) differ between healthy controls and individuals with ALS, decline in physical function should not impact the ability of an individual to use a BCI system.

4.2 Technique

To determine whether P300 signals are adequately detected by a commercial electrode cap, an electrode test system will be designed for use prior to subject use of the BCI system. This test system will allow the session administrator to determine whether each of the 8 electrodes is functioning at full capacity.

The P300 Speller and BCI2000 [8] will be used to evaluate an individual's ability to communicate using a P300-based BCI as determined through spelling accuracy. Analysis will be completed in MATLAB to determine individual and group characteristics of the P300 waveform across 8 electrode channels.

5. DEVELOPMENT OF A TEST SYSTEM

5.1 Rationale

The goal of the electrode test system is to design a device which allows each electrode to be examined for functionality. If electrodes are broken or functioning incorrectly, unnecessary testing or subject frustration with the system may result.

5.2 Design

The electrode test system should be able to acquire and reproduce signals from a signal generator. It should be flexible such that a subject already wearing the electrode cap could perform the testing without harm. As shown in Figure 9, a signal generator is attached to the electrodes embedded in the commercial cap through individual wires. Each electrode sends a signal output to the DATAQ acquisition box, which translates the signal to acquisition software on a computer. The signal can then be stored for further analysis.

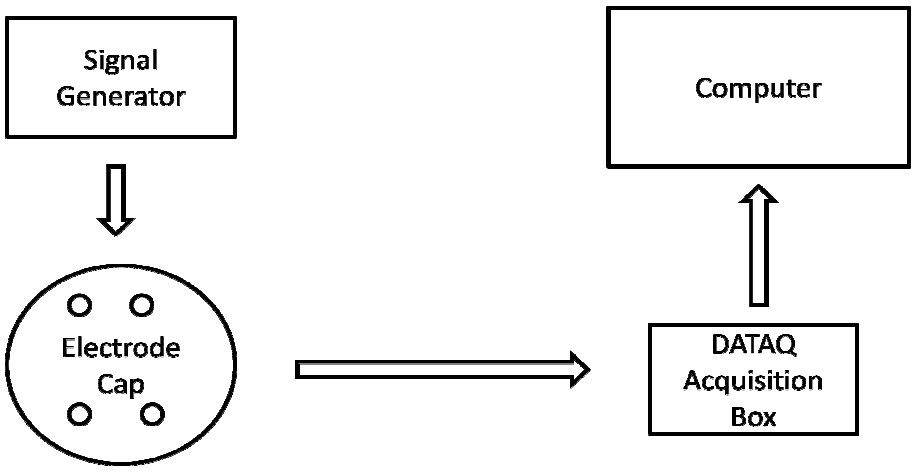

Figure 9: Block diagram of an electrode test system

5.2.1 Testing a Single Electrode

A signal passed through an individual electrode should be visible from a data acquisition system. A single electrode was disconnected from the electrode cap and placed in the system as shown in Figure 9. The incoming wire was attached to a signal generator producing a sine wave. Because an electrode in the cap is connected to both a reference and a ground, the single electrode was grounded to the DATAQ signal acquisition box and referenced to a second electrode. A picture of the single electrode setup is shown in Figure 10.

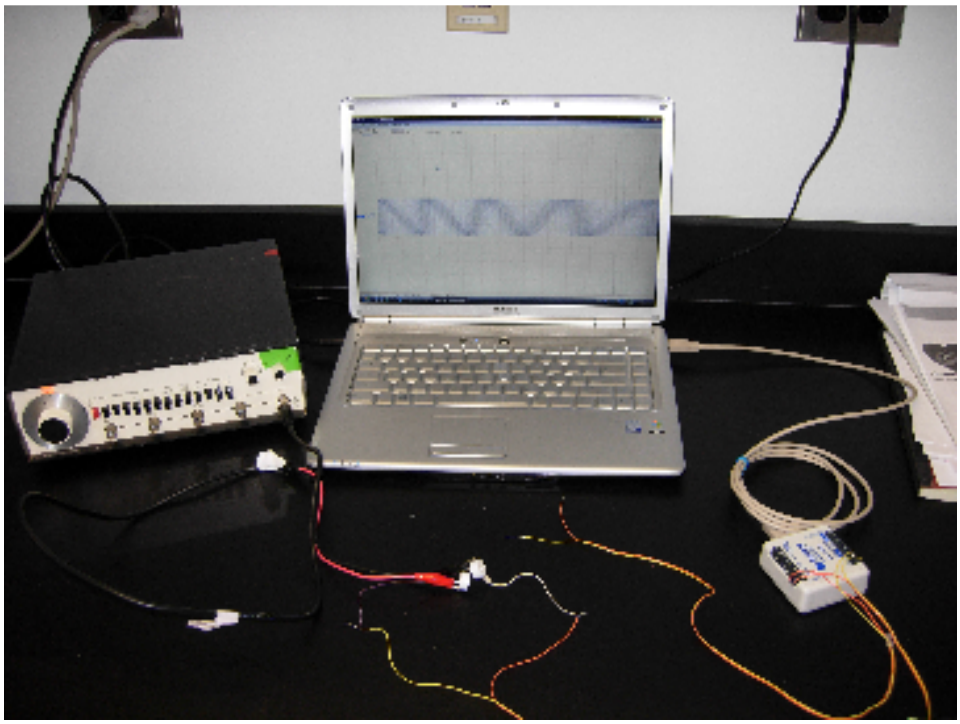

Figure 10: Testing setup for a single electrode system.

5.2.2 Testing of the Electrode Cap

To test the entire electrode cap for functionality, all 10 electrodes (8 signal, 1 ground, and 1 reference) should be attached to the DATAQ signal acquisition box. However, the DATAQ box

only allows for 4 inputs. Thus, for the purposes of this initial system design, only 4 channels were tested. All 10 channels could be tested by moving the leads to additional locations on the cap.

The incoming wires to the electrodes were attached to a signal generator producing a sine wave at amplitude of 2 V peak to peak and frequency of 1 Hz as shown in Figure 9. The 4 electrodes were grounded to the DATAQ signal acquisition box. All electrodes remained in the cap for the duration of the testing to ensure that a subject would be able to wear the cap and perform the test at the same time. A picture of the 4 electrode test system is shown in Figure 11.

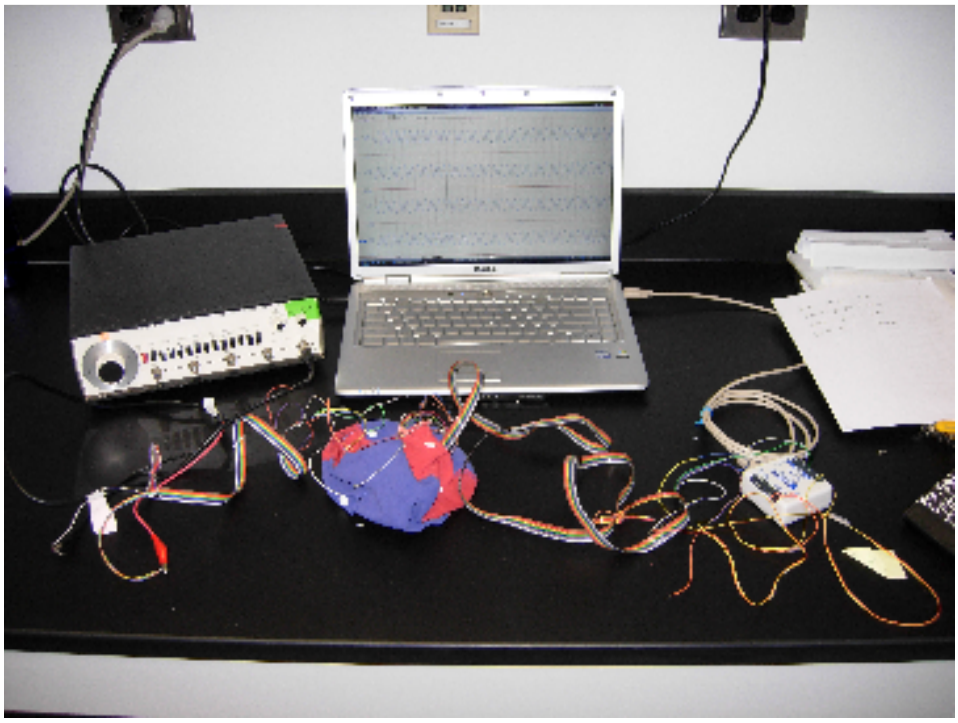

Figure 11: Testing setup for a 4 electrode system.

6. METHODS

6.1 Subjects

Four able-bodied and eight individuals with ALS from the Philadelphia community participated in the trials. One user had previous experience with the P300 Speller paradigm. The study was approved by the Drexel University College of Medicine Institutional Review Board, and each user gave informed consent. If the subject was unable to sign his/her own consent, it was signed by a legally authorized representative. The subject's acceptance of the consent was determined through a traditional yes/no response as reported by the legally authorized representative. The approved consent is presented in Appendix B.

6.2 Data Acquisition and Signal Processing

EEG was recorded using a cap (Electro-Cap International, Inc.) embedded with 8 electrodes distributed according to a modified International 10-20 system. The size of the cap used was based on the circumference of the subject's head. All 8 channels were grounded to the right mastoid and referenced to the left mastoid. The EEG signal was bandpass filtered 0.1-60 Hz, amplified with a Guger Technologies amplifier (20,000x), digitized at a rate of 240 Hz, and stored. All aspects of data collection were controlled by the BCI2000 system [8].

6.3 Task, Procedure, and Experimental Design

The subject was positioned approximately 1 meter from a computer screen to view the matrix display. In cases where the individual was restricted to a wheelchair or a bed the subject was made as comfortable as possible and the screen was positioned for ease of viewing. A 6 x 6

matrix consisting of white characters on a black background was displayed on the screen. An example setup is shown in Figure 12.

a  b 

Figure 12: BCI setup for (a) the individual wearing the electrode cap and (b) the viewing screen, computer system, and amplifier.

Each subject was fitted with an electrode cap. Each electrode was injected with electrode gel (Electro-Cap International, Inc.) until the impedance was below 10 kΩ as shown in Figure 12a.

The user's task was to complete a copy-spelling session in which the target letter is specified to allow for offline analyses. The user was asked to focus attention on one letter of the matrix and count the number of times the row or column displaying that target letter was intensified. The rows and columns of the matrix were intensified in a random sequence such that each of the 6 rows and 6 columns were intensified once before any were repeated. At the start of each run, the first letter of a word was presented in parentheses at the end of the word. This letter was the target letter. After 14 row and column intensifications (epochs) the classifier made a decision on the letter chosen. The sample rate was 256 Hz. There was a 4 second (s) delay before and after

the test sequence began with a stimulus duration of 3 sample blocks and an inter-stimulus interval of 4 sample blocks[3]. After a 2.5 s delay, the letter is reported to the administrator of the test. An additional 2.5 s later the next character in the word was presented in parentheses (for a total time between characters of 5 s). This process continued until the entire word was spelled. The sentence "THE QUICK BROWN FOX JUMPS OVER THE LAZY DOG" was spelled completely for classification. The subject was not given the opportunity to correct for any mistakes. For a detailed protocol, refer to Appendix C.

6.3.1 P300 Spelling Accuracy

The ability of an individual to use the system can be judged by the number of letters correctly selected by the subject out of the phrase "OVER THE LAZY DOG." The percent correct is the number of letters chosen correctly divided by the number of letters in the phrase (14), multiplied by 100 [9, 10].

6.3.2 P300 Spelling Accuracy Given a Change in Electrode Location

Further experimentation was done on 4 subjects in whom the ground and reference mastoids were placed (1) on the left and right mastoid, (2) directly below the ear, and (3) 5 cm below the ear on the lower neck. The subject was asked to complete a copy-spelling session by spelling "THE QUICK BROWN FOX JUMPS" with the electrodes in each of the three locations. The predicted percent correct and number of flashes to achieve this percentage were recorded.

The Coefficient of Variance (CV) was computed for each subject. It is defined as the ratio of the standard deviation to the mean of the data. A CV less than 0.15, or 15%, indicates acceptable variance in moving the electrodes.

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[3] In runs for BCI015 and all runs for electrode placement testing the stimulus duration was changed to 6 sample blocks and the inter-stimulus interval was changed to 2 sample blocks.

6.3.3 Analysis of the P300 Waveform

Analysis of the P300 waveforms was conducted using the MATLAB P300 GUI in the BCI2000 software [23] as well as the MATLAB Offline Analysis program [8]. Maximum amplitude is defined as the maximum positive amplitude value which the waveform takes over an 800 ms interval for a specific channel.

The coefficient of determination (r^2) value is a statistical measure which calculates the fraction of the total signal variance that is accounted for by the spelling task. Maximum r^2 value is defined as the maximum r^2 value which the waveform takes over an 800 ms interval for a specific channel.

A two-tailed two-sample t-test was used to determine whether differences in latency and amplitude in the P300 signal between controls and individuals with ALS were significant ($p<0.05$). In examining the latency of the P300 signal, a preliminary test for the equality of variances indicated that the variances of the two groups were significantly different ($F=5.246$, $p=.033$). Therefore, a two-sample t-test was performed that assumed unequal variances. In examining the amplitude of the P300 signal, a preliminary test for the equality of variances indicated that the variances of the two groups were not significantly different ($F=0.621$, $p=.377$). Therefore, a two-sample t-test was performed that assumed equal variances.

7. RESULTS

7.1 Test System

The electrode test system can be used to determine whether electrodes are functioning properly before a subject uses the cap. Figure 13 shows the first 100 data points obtained from the DATAQ acquisition software. A longer duration of signal acquisition is shown in Appendix D.

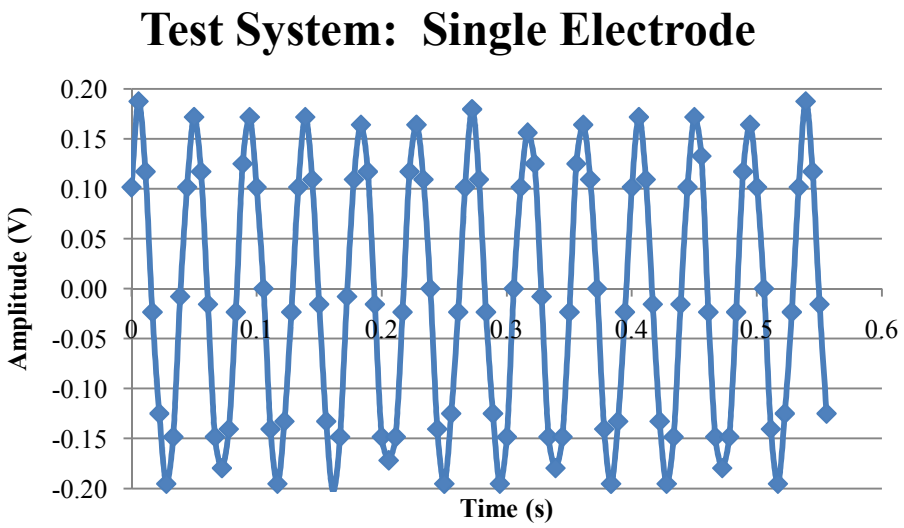

Figure 13: Amplitude of a sine wave signal in a single electrode over time for the designed test system.

Figure 14 shows the first 100 data points obtained from the DATAQ acquisition software for Channels 5, 6, 7 and 8 (the four channels chosen for testing purposes). The peak to peak voltage for this time period is 1.89 V for Channels 5, 6 and 7 and 1.88 V for channel 8. A longer duration of signal acquisition is shown in Appendix D.

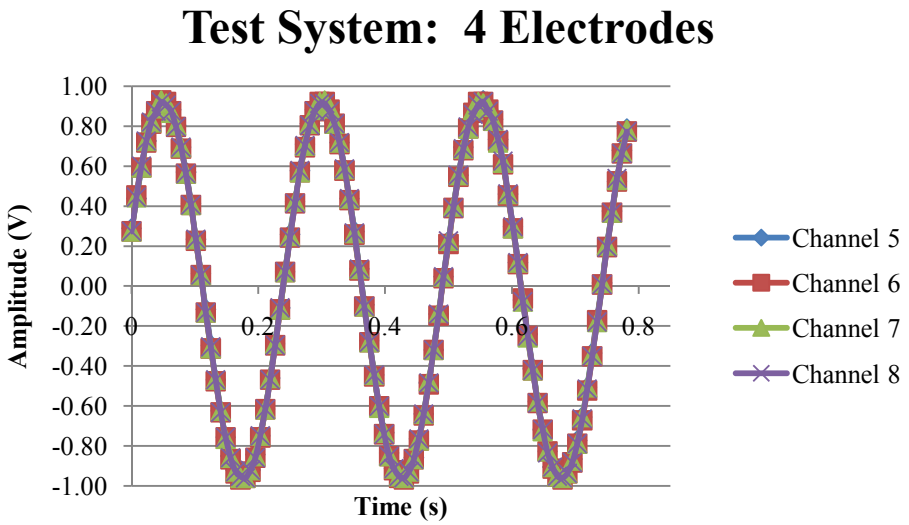

Figure 14: Amplitude of a sine wave signal in Channels 5, 6, 7, and 8 over time for the designed test system.

7.2 P300 Spelling Accuracy

The ability of an individual to use the system can be judged by the number of letters correctly selected by the subject out of a set sequence of letters. The subject number, gender, age, diagnosis, ALSFRS score (if applicable) and percent correct for all subjects is shown in Table 1. See Appendix E for an extended table indicating date of symptom onset, date of diagnosis, and medications.

Table 1 Spelling accuracy as determined by percent correct for all subjects.

Subject	Gender	Age	Diagnosis	ALSFRS	Percent Correct
BCI004	M	55	ALS	18	93
BCI006	M	54	ALS	27	86
BCI007	F	66	ALS	27	71
BCI008	F	57	ALS	33	64
BCI009	M	54	ALS	1	100
BCI011	F	48	ALS	34	100
BCI012	M	50	ALS	1	79
BCI013	M	38	ALS	11	100
BCI001	F	43	Control	NA	100
BCI002	M	24	Control	NA	100
BCI003	M	22	Control	NA	86
BCI014	M	23	Control	NA	100

The ALSFRS is commonly used to indicate disease progression. Figure 15 demonstrates the spelling accuracy of the subject as indicated by the percent correct as a function of the ALSFRS score of the subject. Controls are excluded from this analysis as all controls have full functionality in daily activities.

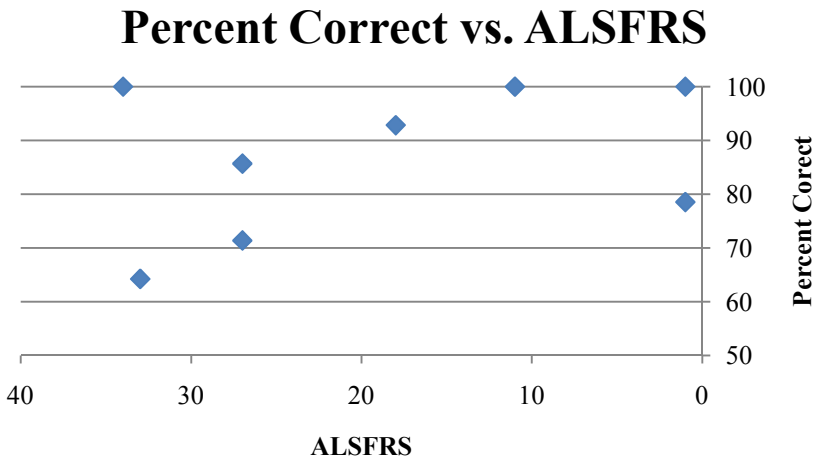

Figure 15: Spelling accuracy as indicated by percent correct vs. ALSFRS.

Changes occur in the brain as an individual ages. Figure 16 shows spelling accuracy as a function of subject age for all subjects. Males are indicated with a blue diamond while females are indicated with a red square.

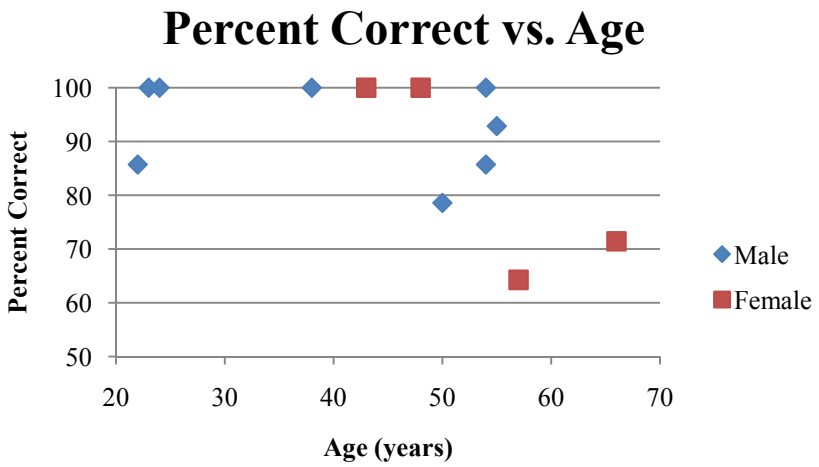

Figure 16: Spelling accuracy as indicated by percent correct vs. subject age.

7.3 P300 Spelling Accuracy Given a Change in Electrode Location

Table 2 shows the predicted percent correct and the number of epoch flashes to achieve that accuracy as determined by the BCI2000 software. Data is presented for all electrode locations for which the subject participated in the trial. Peak values are shown in Appendix G.

Table 2: Predicted percent correct spelling and the number of flashes to achieve accuracy based on ground and reference electrode location in healthy controls and individuals with ALS.

Subject	Disease State	Position	Predicted Percent Correct	Number of Flashes
BCI006	ALS	1	100	13
BCI006	ALS	2	95	10
BCI006	ALS	3	90	13
BCI012	ALS	1	90	13
BCI012	ALS	2	90	11
BCI012	ALS	3	100	7
BCI014	Control	1	100	3
BCI014	Control	2	100	7
BCI014	Control	3	100	5
BCI015	Control	1	100	6
BCI015	Control	2	100	4

Table 3 indicates the CV for both controls and ALS subjects. The CV for the latency of the peak amplitude of the P300 signal, peak amplitude of the P300 signal, and peak r^2 value of the P300 signal are calculated.

Table 3: CV values for all subjects for the latency, peak amplitude, and peak r^2 value of the P300 signal.

Subject	Latency	Peak Amplitude	Peak r^2
BCI006	0.152	0.144	0.518
BCI012	0.386	0.125	0.344
BCI014	0.289	0.125	0.059
BCI015	0.495	0.077	0.573

7.4 Analysis of the P300 Waveform

The r^2 plot demonstrates the fraction of the total signal variance that is accounted for by the spelling task. Here, condition 1 is the presence of a target letter and condition 2 is the presence of a non-target letter. Figure 17 shows the r^2 values over 1000 ms and 8 channels for control subject BCI001.

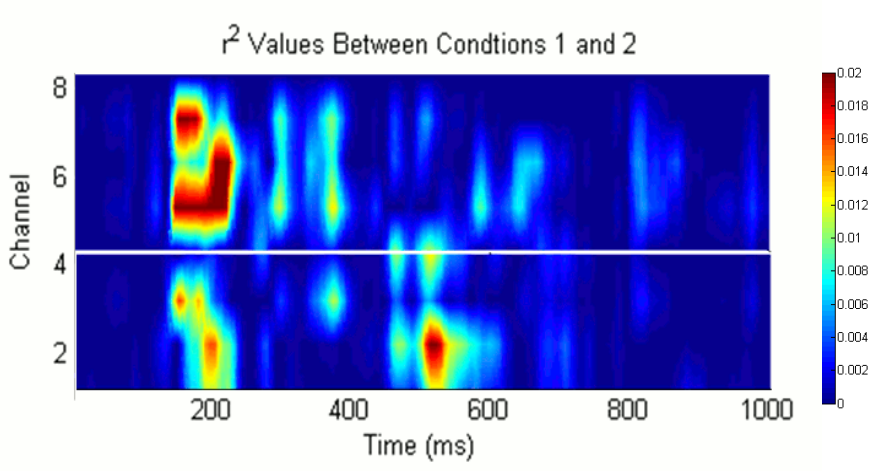

Figure 17: r^2 plot for control subject BCI001.

Analysis of the r^2 values can also be performed across individual electrode channels. Figure 18 shows the amplitude of the P300 signal and the statistical measure r^2 between the target (red) and non-target (green) letter for control subject BCI001 over 800 ms. Channels 13, 14, 15, and 16 correspond to Channels 5, 6, 7, and 8, respectively in Figure 17.

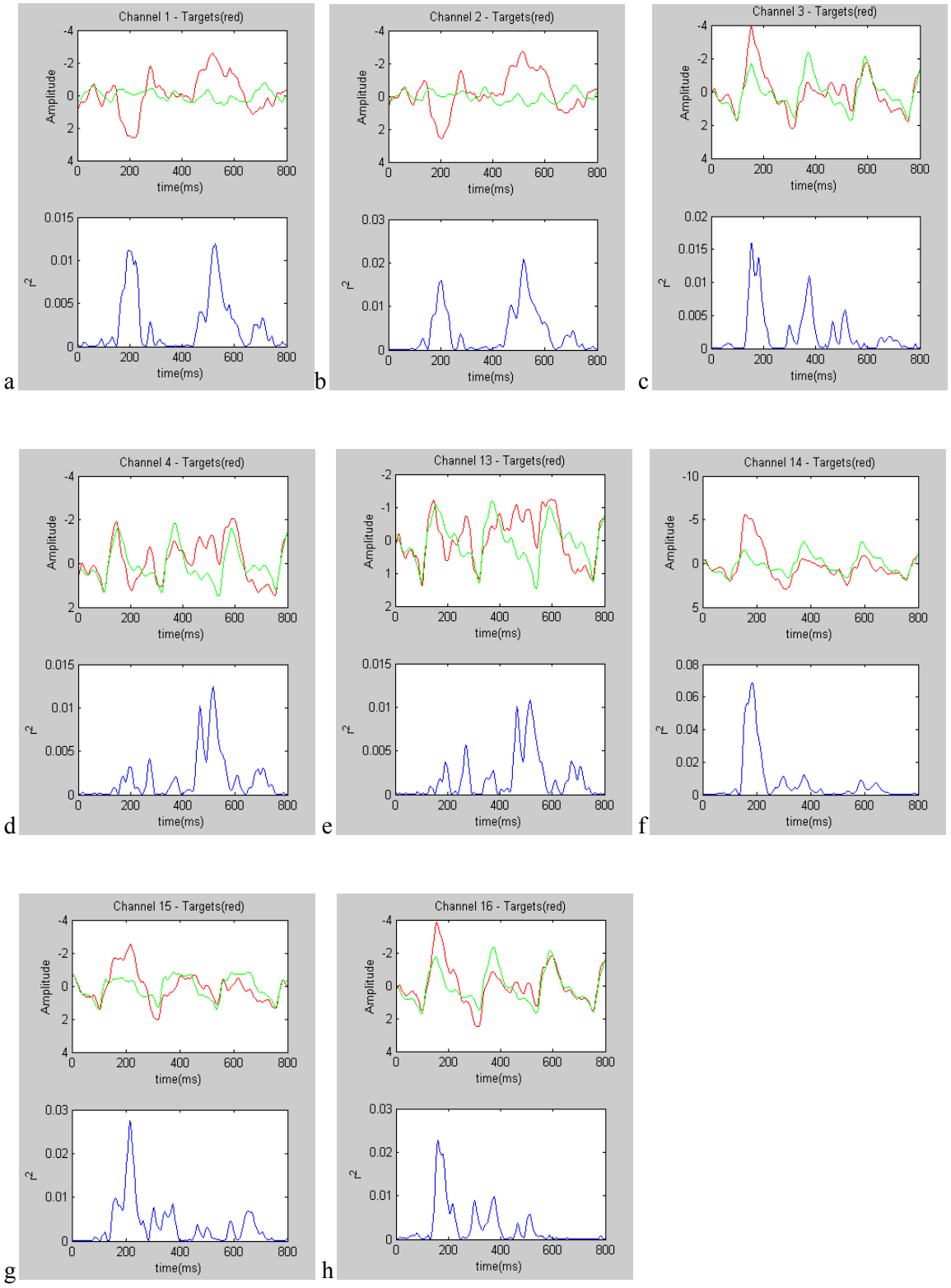

Figure 18: Individual waveforms for control subject BCI001 for (a) Channel 1, (b) Channel 2, (c) Channel 3, (d) Channel 4, (e) Channel 5, (f) Channel 6, (g) Channel 7, and (h) Channel 8.

Figure 19 shows the r^2 values over 1000 ms and 8 channels for ALS subject BCI004.

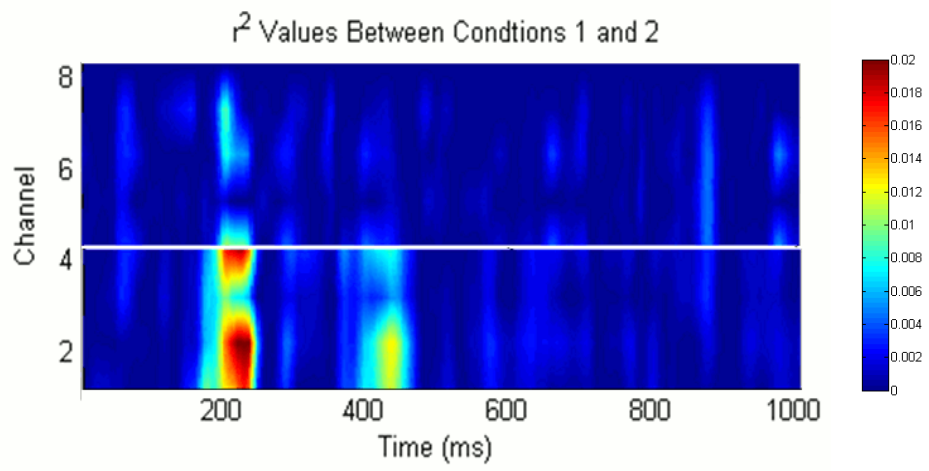

Figure 19: r^2 plot for ALS subject BCI004.

Figure 20 shows the amplitude of the P300 signal and the statistical measure r^2 between the target (red) and non-target (green) letter for ALS subject BCI004 over 800 ms. Channels 13, 14, 15, and 16 correspond to Channels 5, 6, 7, and 8, respectively in Figure 19.

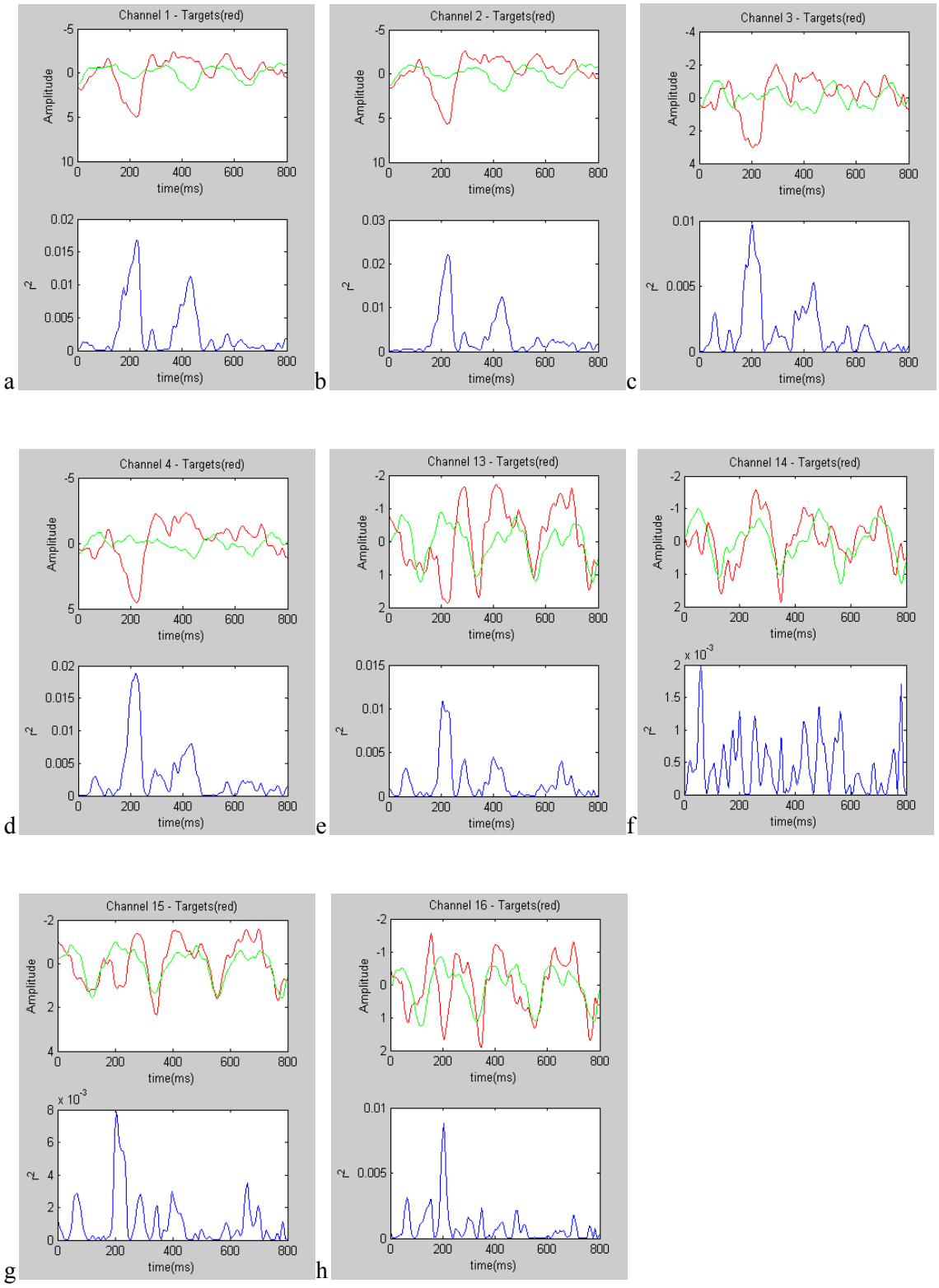

Figure 20: Individual waveforms for ALS subject BCI004 for (a) Channel 1, (b) Channel 2, (c) Channel 3, (d) Channel 4, (e) Channel 5, (f) Channel 6, (g) Channel 7, and (h) Channel 8.

Control subject BCI001 and ALS subject BCI004 are presented as representative data from the two subject groups. The r^2 plots and individual waveforms are presented for all subjects in Appendix F. Appendix G contains a listing of the peak amplitude, r^2 value and time by channel for each subject.

A two-sample t-test was performed to test the null hypothesis that there was no difference in the latency of the peak amplitude of the P300 signal in controls and individuals with ALS. The mean latency for controls (M=301.75, SD=49.21, N=4) was significantly later than the mean latency for individuals with ALS (M=205.08, SD=21.49, N=8) using the two-sample t-test for unequal variances, $t(4)=2.78$, $p=0.020$.

A two-sample t-test was performed to test the null hypothesis that there was no difference in the peak amplitude of the P300 signal in controls and individuals with ALS. The mean peak amplitude for controls (M=3.02, SD=1.06, N=4) was not significant when compared to the mean peak amplitude for individuals with ALS (M=4.07, SD=1.34, N=8) using the two-sample t-test for equal variances, $t(10)=2.23$, $p=0.20$.

8. DISCUSSION

8.1 Test System

The initial test system consists of a single electrode attached to a signal generator and data acquisition system. It is important that the electrode be able to maintain an alternating current (AC) signal, as the signal generated in the brain and elucidated with EEG is alternating in nature. Figure 13 shows that a single electrode can in fact be used to record a continuous AC signal as a sine wave signal can be viewed with the data acquisition software.

With this signal acquisition, it was then possible to extend the system to cover 4 electrodes at once and determine the actual capabilities of the electrodes. Figure 14 shows the consistency in the applied signal over the 4 examined electrodes. Appendix D shows that the electrodes can adjust to changes in signal amplitude. Thus, as changes occur to the signal within the brain, the electrodes are able to adapt and report back an adequate response.

Peak to peak voltages indicate that 6% of the signal is lost in channels 5, 6, and 7 and 5% of the signal is lost in channel 8. This loss demonstrates that while the electrodes are sensitive there is some signal loss, which may cause EEG to lose part of a signal arising from the brain.

One limitation of this test system was the DATAQ acquisition box. A larger box consisting of 10 channels would allow all electrodes to be tested at once. In order for such a test system to be used in a home or clinic setting it must be possible to test all of the electrodes simultaneously. Another limitation was the inability to read the signal with the available EEG software. Additional studies must be performed to test the ability of EEG to read a signal generated external to the brain.

8.2 P300 Spelling Accuracy

An individual is considered to be a responder if he/she obtains 75% spelling accuracy. This is the minimum percentage deemed necessary to understand communication efforts. All controls were responders, with the lowest ability at 86%. This indicates that the system does work in a healthy population. Only 2 individuals with ALS were non-responders (BCI008 and BCI007 at 64% and 71%, respectively). Therefore, the majority of individuals with ALS were able to use the BCI system effectively.

There is no correlation between spelling ability and ALSFRS. Thus, individuals who are extremely disabled are still able to use the BCI. However, it is important to note that the ALSFRS does stop at a particular point and many individuals continue to survive and progress past an ALSFRS score of 1 or 0. Therefore, to truly evaluate disease progression and its effects on spelling ability, a new scale or method of monitoring disease progression should be created beyond the ALSFRS.

In combining healthy controls and individuals with ALS, there is no correlation between spelling ability and age in either males or females. All individuals are able to use the system which shows that although brain function may change over time, the brain is consistently able to obtain a P300 response.

8.3 P300 Spelling Accuracy Given a Change in Electrode Location

Healthy controls were able to obtain 100% spelling accuracy in all ground and reference electrode locations with a maximum of 7 flashing sequences. Both individuals with ALS were considered responders at all locations but only obtained 100% accuracy at one location (location 1 for BCI006 and location 3 for BCI012).

The ability to accurately use the system with changes in the placement of ground and reference electrodes and the number of flashing sequences demonstrates that the system does not need to be static.

Table 2 shows that the ideal location and number of sequences will be individualized, and can be changed to fit individual preferences and capabilities. The ability to move these electrodes allows greater comfort for individuals who wear glasses or are extremely disabled and must communicate from a bed or wheelchair. The ability to reduce the number of flashing sequences provides faster communication. Greater overall comfort and satisfaction ensures that the individual is more willing to use the BCI as an option for communication.

For all subjects the CV for the latency of the peak amplitude was significant and the CV for the peak amplitude was not significant. This indicates that although the different electrode locations showed spikes in the P300 signal at different times, the peak amplitude remained consistent. Therefore, an individual does have stability in P300 amplitude. With the exception of subject BCI014, the CV for the peak r^2 value varies significantly across electrode locations. This possibly shows that although the target amplitude remains the same across locations, there are differences in the way the target and non-target signals are characterized.

8.4 Analysis of the P300 Waveform

Figure 17 and Figure 19 were chosen as representative r^2 plots for a healthy control and an individual with ALS, respectively. In general, individuals with ALS show lower r^2 values across the 8 electrode channels. In 3 out of the 4 healthy controls, activity can be visualized across all electrodes. However, in 7 out of the 8 individuals with ALS, activity can be visualized primarily in Channels 1-4. This difference does not, however, inhibit the ability of an individual with ALS to accurately use the P300 Speller.

Examination of the individual waveforms (such as those in Figure 18 and Figure 20) further shows the differences between subjects. In some cases the waveforms are clean with consistent spikes indicating the response to a target letter. In other individuals the waveforms appear to have a great deal of noise or EEG artifacts and it may be difficult to determine with certainty when the target letter is being selected.

A two-sample t-test revealed that the latency of the peak amplitude P300 signal was significantly later in healthy controls than individuals with ALS. Although the P300 is defined as the peak amplitude between 220 and 500 ms, the healthy controls had a mean latency of 301.75 ms, indicating that controls are able to identify the target letter and obtain a regular brain response. With a mean latency of 205.08, individuals with ALS respond faster to target stimuli. This may indicate a difference in brain structure or electrical wiring within the brain which causes the response to be processed more quickly.

A second two-sample t-test showed that the peak amplitude of the P300 signal was not significantly different between healthy controls and individuals with ALS. Thus, although the latency may change, the amplitude response to target stimuli does not. The same level of excitement is elicited in both controls and individuals with ALS.

9. CONCLUSIONS AND RECOMMENDATIONS TO THE FIELD

Individuals with ALS are able to use the P300-based BCI for communication. Spelling ability is not correlated with ALSFRS or age, indicating that individuals of all ages and levels of disability may be able to use the system. In addition, testing the ability to move the ground and reference electrodes demonstrates the flexibility of the system. This allows for greater comfort and satisfaction with the system as a communication tool.

There are differences in the signals produced by healthy controls and individuals with ALS. The latency of the peak amplitude P300 signal was significantly later in controls compared to individuals with ALS. On the other hand, the peak amplitude itself was not significantly different. This examination shows that there may be differences in electrical wiring within the brains of individuals with ALS. These differences do not, however, translate to an inability to use the BCI for communication.

The BCI2000 system has been tested numerous times in healthy and disease populations. Therefore, the main approach to this study was to assume that the BCI system worked well and could accurately classify EEG signals. Differences between healthy controls and individuals with ALS provide further motivation to study the system in a disease population and create mock systems.

The original design of the test system is adequate for determining functionality and flexibility of the individual electrodes. In order to be a true mock system, coils should be used to induce a signal. This would more accurately reflect the signal arising through the skull to the electrode surface. Designing a mock skull would allow the researcher to test different issues in brain

functionality and different disease conditions. This may allow the researcher to determine the feasibility of a diseased individual using the BCI without testing the BCI on the individual.

To fully understand the differences between healthy controls and individuals with ALS additional data should be collected. In particular, a wider range of disease states and more individuals who are locked-in should be examined. Additional data will help to determine whether differences are individual or based on disease with certainty.

Work with locked-in individuals demonstrates the need for early implementation of the BCI. Individuals with ALS should be screened on a regular basis (every 6 months or once a year, depending on disease progression) to determine their ability to achieve spelling accuracy. Once an individual becomes locked-in it is difficult to determine whether he/she understands how to use the system. Early screening will ensure that the use of the system is understood. In addition, collection of data on a regular basis across various levels of disease progression would help to track changes in brain function over time.

Perhaps the most important recommendation to the field comes directly from the individuals using the system. Caregivers often assume that individuals wish to communicate their daily needs. While this is true, people also want to be able to communicate their desires and, most importantly, to have regular discussions with their loved ones. It is important that in addition to focusing on the technology, researchers also examine patient comfort and ease of use. The ideal BCI will be easy to understand, easy to implement, and will allow the individual freedom to control their world as they were once able to do.

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APPENDIX A: ALS FUNCTIONAL RATING SCALE

1. SPEECH 4 Normal speech processes 3 Detectable speech disturbance 2 Intelligible with repeating 1 Intelligible with non-vocal communication 0 Loss of useful speech	8. WALKING 4 Normal 3 Early ambulation difficulties 2 Walks with assistance 1 Non-ambulatory functional movement only 0 No purposeful leg movement
2. SALIVATION 4 Normal 3 Slight but definite excess saliva in mouth; may have night time drooling 2 Moderately excessive saliva; may have minimal drooling 1 Marked excess of saliva with some drooling 0 Marked drooling; requires constant tissue or handkerchief	9. CLIMBING STAIRS 4 Normal 3 Slow 2 Mild unsteadiness or fatigue 1 Needs assistance 0 Cannot do
3. SWALLOWING 4 Normal eating habits 3 Early eating problems-occasional choking 2 Dietary consistency changes 1 Needs supplemental tube feeding 0 NPO	
4. HANDWRITING 4 Normal 3 Slow or sloppy; all words legible 2 Not all words are legible 1 No words are legible, but can still grip pen 0 Unable to grip pen	ALSFRS-R Respiratory Subscale The following questions are to be asked after completion of the main portion of the ALSFRS (questions 1-10)
5a. CUTTING FOOD AND HANDLING UTENSILS Subjects without gastrostomy. 4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can cut most foods, although slow and clumsy; some help needed 1 Food must be cut by someone, but can still feed slowly 0 Needs to be fed	R-1. DYSPNEA 4 None 3 Occurs when walking 2 Occurs with one or more of the following: eating, bathing, dressing (ADL) 1 Occurs at rest; when either sitting or lying 0 Significant difficulty, considering using mechanical respiratory support
5b. CUTTING FOOD AND HANDLING UTENSILS Subjects with gastrostomy. 4 Normal 3 Clumsy, but able to perform all manipulations independently 2 Some help needed with closures and fasteners 1 Provides minimal assistance to caregiver 0 Unable to perform any aspect of the task	R-2. ORTHOPNEA 4 None 3 Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows 2 Needs extra pillows in order to sleep (more than two) 1 Can only sleep sitting up 0 Unable to sleep
6. DRESSING AND HYGIENE 4 Normal function 3 Independent self care with effort or decreased efficiency 2 Intermittent assistance or substitute methods 1 Needs attendant for self-care 0 Total dependence	R-3. RESPIRATORY INSUFFICIENCY 4 None 3 Intermittent use of BiPAP 2 Continuous use of BiPAP during the night 1 Continuous use of BiPAP during day and night 0 Invasive mechanical ventilation by intubation or tracheotomy
7. TURNING IN BED AND ADJUSTING BED CLOTHES 4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can turn alone or adjust sheets, but with great difficulty 1 Can initiate, but not turn or adjust sheets alone 0 Helpless	ALSFRS Score _____/48

APPENDIX B: IRB APPROVED PROTOCOL

Drexel University College of Medicine

Consent to Take Part In a Research Study

1. **Subject Name:**
   _____

2. **Title of Research: EEG-Based Brain-Computer Interface Project for Individuals With ALS**

3. **Investigator's Name:** Terry Heiman-Patterson, MD

4. **Research Entity: This research study is being done by a researcher of the Philadelphia Health & Education Corporation, which does business under the name Drexel University College of Medicine. Drexel University is a separate corporation and is not involved in or a party to this research study.**

5. **Consenting for the Research Study: This is a long and an important document. If you sign it, you will be authorizing Drexel University College of Medicine and its researchers to perform research studies on you. You should take your time and carefully read it. You can also take a copy of this consent form to discuss it with your family member, physician, attorney or anyone else you would like before you sign it. Do not sign it unless you are comfortable in participating in this study.**

6. **YOUR RIGHT TO PRIVACY AND CONFIDENTIALITY: Very specific information on your right to privacy and the confidentiality of the use and disclosure of your personal health information can be found at the end of this consent form. We need your authorization to use and disclose the health information that we may collect about you during this research study. To be in this research study you must read and sign the authorization at the end of this consent form.**

7. **PURPOSE OF RESEARCH:**
   You are being asked to participate in a research study. The purpose of this study is to investigate if using EEG-based Brain Computer Interface technology is a suitable and reasonable choice as a communication solution for individuals with ALS. You are being asked to participate either as an individual with a diagnosis of probable or definite ALS, or as a control subject. ALS is a disease that affects the nerves which control muscles. As the disease progresses the nerves die and the patients loose their ability to control the muscles movements. In this project we are trying to see if this new technology will be a helpful method of communication for ALS patients.
   EEG-based Brain Computer Interface technology uses the EEG to help click on the setup area (like a computer mouse and keyboard) to spell or press certain buttons, that will aid communication.

The control subjects will help us find out whether any hardship in doing the test is due to the disease or the technique itself. Your decision to either participate or not to participate will not influence your medical care or any further medical treatment you may need. Approximately 50 people, between the ages of 18 to 90 years, will be asked to participate in this study.

8. **PROCEDURES AND DURATION:**

You understand that all of the following things that will be done to you are experimental.
The initial training will be conducted in an exam room in the Neurology outpatient clinic.
If you participate in the study, you understand that you will be asked to do the following things:

a) **You will be asked to fill out a questionnaire and be evaluated by a functional rating scale. This functional scale asks questions about how you are able to take care of yourself. This will take about five minutes.**
b) **Next, your EEG, or brainwaves, will be recorded. To do this, you will sit in a comfortable chair or your own wheelchair approximately 3 feet away from a computer monitor. Up to 64 scalp electrodes will be placed on your head, the electrodes are pre-fixed in an electrode cap (e.g., Electro-Cap, Inc.). A small amount of an odorless, colorless, water-soluble gel is applied to each electrode. The only discomfort you may experience during this procedure is the transient coolness of the gel. You will not feel anything unusual during the recording. The electrodes can be placed directly over your hair. There is no need to shave the area.**
c) **You will then be asked to follow a series of instructions while the EEG is being recorded. These instructions include; counting the number of times a particular letter or symbol is seen on the screen or count the number of times a particular tone is heard. Like most standard noninvasive electroencephalograms (EEGs), our procedure takes between one and one and one half hours including set up and clean up. Water, shampoo, a towel and hair dryer will be provided if you wish to remove the gel at the end of the session.**
d) **Following this session, you will be asked to return for one more training and recording sessions, similar to the first. You may also be asked if you would like to continue with further training and recording sessions in your home. You will decide on how many sessions you need to feel comfortable with using the machine. These sessions at home will also be similar to the outpatient clinic sessions and will take about one and one half hours.**
e) **If you already use a communication device, you may be requested to copy the same activity with your usual means of communication for time, efficiency, and proficiency comparisons.**

You may withdraw at any time.

The data gathered will also be sent to our collaborating site, Wadsworth Center, for data analysis.

9. **RISKS AND DISCOMFORTS/CONSTRAINTS:**

The BCI system uses clinical-grade equipment. Thus, the study risk is no greater than the extremely small risk associated with routine clinical EEG recording. The only discomfort you may experience during this procedure is the transient coolness of the gel.

We will try to accommodate and have you either sitting up or semi-reclined to make you comfortable during the test. However, if you do need to move or change position, the test will be stopped until you are ready to start.

10. **UNFORESEEN RISKS:**
Participation in this study may include unforeseen risks. If unforeseen risks are seen, they will be reported to the Office of Regulatory Research Compliance.

11. **BENEFITS:**
There may be no direct benefits to you from participating in this study.

12. **ALTERNATIVE PROCEDURES/TREATMENT:**
The alternative is <u>not</u> to participate in this study.

13. **REASONS FOR REMOVAL FROM STUDY:**
You may be required to stop the study before the end for any of the following reasons:
    a) **Change in medical condition;**
    b) **If all or part of the study is discontinued for any reason by the investigator, university authorities, or government agencies; or**
    c) **Other reasons, including new information available to the investigator or harmful unforeseen reactions experienced by the subject or other subjects in this study.**

14. **VOLUNTARY PARTICIPATION:**
You understand that being in this study is voluntary for the ALS subjects as well as the controls. Your health care will not be affected in any way if you decline to be in or later withdraw from the study. You can refuse to be in the study or stop at any time without the loss of the care benefits to which you are entitled if you should suffer an injury as result of this trial.

15. **RESPONSIBILITY FOR COST**
You will not be responsible for the costs of the procedures strictly related to this study. You will not receive any payment for taking part in this study.

16. **IN CASE OF INJURY:**
Treatment for Injury: If you have any questions or believe you have been injured in any way by being in this research study, you should contact Dr. Terry Heiman-Patterson, MD at telephone (215)-762-5186. However, no payment or compensation will be provided for injury, illness or other loss resulting from your being in this research study. If you are injured by this research activity, medical care including hospitalization is available, but may result in costs to you or your health insurance. If you are injured or have an adverse reaction, you should also contact the Office of Regulatory Research Compliance 215-255-7857.

17. **CONFIDENTIALITY AND PRIVACY:**
This section gives more specific information about the privacy and confidentiality of your health information. It explains what health information about you will be collected during this research study and who may use, give out and receive your health information. It also describes your right to inspect your medical records and how you can revoke this authorization after you sign it.

By signing this form, you agree that your health information may be used and disclosed during this research study. Your health information may be disclosed or transmitted electronically. We will only collect information that is needed for the research study. Your health information will only be used and given out as explained in this consent form or as permitted by law.

In any publication or presentation of research results, your identity will be kept confidential.

A. Individually Identifiable Health Information that will be collected

The following personal health information about you will be collected and used during the research study and may be given out to others:

- **Your name, address, telephone number, date of birth;**
- **Personal medical history;**
- **Information from physical exams and other tests or procedures described in this consent form.**
- **Information learned during telephone calls, surveys, questionnaires and office visits done as part of this research study;**
- **Information in medical records located in your doctor's office or at other medical facilities you may have received treatment.**

B. Who will see and use your health information within Drexel University College of Medicine.

The research study investigator and other authorized individuals involved in the research study at Drexel University College of Medicine will see your health information and may give out your health information during the research study. These include the research investigator and the research staff, the institutional review board and their staff, legal counsel, research office and compliance staff, officers of the organization and other people who need to see the information in order to conduct the research study or make sure it is being done properly.

C. Who else may see and use your health information.

Other persons and organizations outside of Drexel University College of Medicine may see and use your health information during this research study. These include:

- **Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections.**
- **Doctors and staff at other places that are participating in the research study.**
- **The Laboratory of Nervous System Disorders (LNSD) of the Wadsworth Center of the New York State Department of Health will be assisting in coordinating the study and analyzing the data.**

If your health information is given to someone not required by law to keep it confidential, then that information may no longer be protected, and may be used or given out without your permission.

D. Why your health information will be used and given out.
Your health information will be used and given out to carry out the research study and to evaluate the results of the study.

E. If you do not want to give authorization to use your health information.
You do not have to give your authorization to use or give out your health information. However, if you do not give authorization, you cannot participate in this research study.

F. How to cancel your authorization.
At any time you may cancel your authorization to allow your health information to be used or given out by sending a written notice to the Office of Regulatory Research Compliance, 1601 Cherry Street, 3 Parkway, Suite 10444, Philadelphia, Pennsylvania, 19102. If you leave this research study, no new health information about you will be gathered after you leave. However, information gathered before that date may be used or given out if it is needed for the research study or any follow-up.

G. When your authorization ends
Your authorization to use and give out health information will continue until you withdraw or cancel your authorization. After the research study is finished, your health information will be maintained in a research database. Drexel University College of Medicine shall not re-use or re-disclose the health information in this database for other purposes unless you give written authorization to do so. However, the Drexel University College of Medicine Institutional Review Board may permit other researchers to see and use your health information under adequate privacy safeguards.

H. Your right to inspect your medical and research records.
You have the right to look at your medical records at any time during this research study. However, the investigator <u>does not have</u> to release research information to you if it is not part of your medical record.

18. OTHER CONSIDERATIONS:
If you wish further information regarding your rights as a research subject or if you have problems with a research-related injury, for medical problems please contact the Institution's Office of Regulatory Research Compliance by telephoning 215-255-7857.

19. CONSENT:

- **I have been informed of the reasons for this study.**
- **I have had the study explained to me.**
- **I have had all of my questions answered.**
- **I have carefully read this consent form, have initialed each page, and have received a signed copy.**
- **I authorize the use and disclosure of my personal health information as explained in this consent form.**
- **I give consent voluntarily.**

_____ _____

Subject or Legally Authorized Representative **Date**

_____ _____

Investigator or Individual Obtaining this Consent/Permission **Date**

_____ _____

Witness to Signature **Date**

List of Individuals Authorized to Obtain Consent/Permission

Name	Title	Day Phone #	24 Hr Phone #
Terry Heiman-Patterson, MD	**Principal Investigator**	**215-762-5186**	**215-363-0153**
Anahita Deboo, MD	**Co-Investigator**	**215-762-7037**	**215-762-7000**
Sara Feldman, PT	**Key Personnel**	**215-762-5186**	**NA**
Christine Barr, RN	**Key Personnel**	**215-762-5186**	**NA**
Mary Paolone, RN	**Key Personnel**	**215-762-5186**	**NA**

APPENDIX C: DETAILED PROTOCOL

Method 1: Original Electrode Positions

a. System Setup

1. Open BCI2000 and select the P300 speller.
2. Create a 6x6 matrix containing the letters A-Z, Sp (for space), and the numbers 1-9.
3. Measure the circumference of the head to determine which cap size is needed (Red: 54-58 cm, Red/Blue: 56-60 cm, Blue: 59-62 cm).
4. Position the cap so that the current ear holes line up with the ears of the subject. Roll the cap slightly inside out and place the front elastic directly above the eyebrows.
5. Measure the distance between the nasion and Fz electrode. The distance should be approximately 30% of the distance between the nasion and inion.
6. Fill a syringe with electrode gel and place a blunt needle on the tip.
7. Inject approximately 0.5 cc of electrode gel into each of the 8 electrodes. Slowly withdraw the needle while injecting the gel.
8. Examine the impedance of each electrode.
9. Use the blunt end of the Q-tip to move the gel around within the electrode. Inject additional gel onto the scalp. Repeat steps 6 and 7 until the impedance in each electrode is below 10 kohm.

b. Initial Calibration

The initial calibration is used to orient the user to the system and determine initial parameters.

1. Explain the P300 speller to the subject. A word will appear on the screen in yellow with one letter in parentheses. The subject will find the letter in parentheses on the grid and focus on it. Each time the letter turns white (flashes) the subject will count an instance of the letter to himself.
2. Set the first word for the subject to spell to “THE”.
3. Allow the subject to spell the entire first word. Record what the subject has been told to spell and what the computer believes the subject is spelling.
4. Change the word for the subject to spell to “QUICK”.
5. Repeat step 3 until the subject has spelled “THE QUICK BROWN FOX JUMPS”.

c. Initial Parameters

The initial parameters obtained will be used for the secondary calibration.

1. Run P300_GUI in Matlab 2008.
2. Select the 5 complete runs from the initial calibration.
3. Generate feature weights for the initial calibration data.
4. Save the *.mud and *.prm(v2) files.

d. Secondary Calibration

This calibration continues the initial calibration. At this point the system should be able to detect the subject's intent with at least some degree of accuracy.

1. In the BCI2000 program, load the initial parameters.
2. Set the first word for the subject to spell to "OVER".
3. Allow the subject to spell the entire first word. Record what the subject has been told to spell and computer believes the subject is spelling.
4. Change the word for the subject to spell to "THE".
5. Repeat step 3 until the subject has spelled "OVER THE LAZY DOG".
6. Determine the spelling accuracy of the subject. The accuracy will be computed as the number of correct characters displayed divided by the total number of characters (14), multiplied by 100%.

e. Secondary Parameters

The secondary parameters obtained will be used for the spelling test.

1. Run P300_GUI in Matlab 2008.
2. Select the 4 complete runs from the secondary calibration.
3. Generate feature weights for the secondary calibration data.
4. Save the *.mud and *.prm(v2) files.

Method 2: Ground and Reference Electrodes Directly Below the Ear

This method is identical to method one except in the placement of the ground and reference electrodes.

1. Remove the electrodes located on the mastoids from the electrode cap.
2. Center the electrode corresponding to the left mastoid directly below the left ear and the electrode corresponding to the right mastoid directly below the right ear. Secure with medical tape if necessary.
3. Run the test sequence as specified previously for Initial Calibration and Initial Parameters.

Method 3: Ground and Reference Electrodes 5 cm Below the Ear

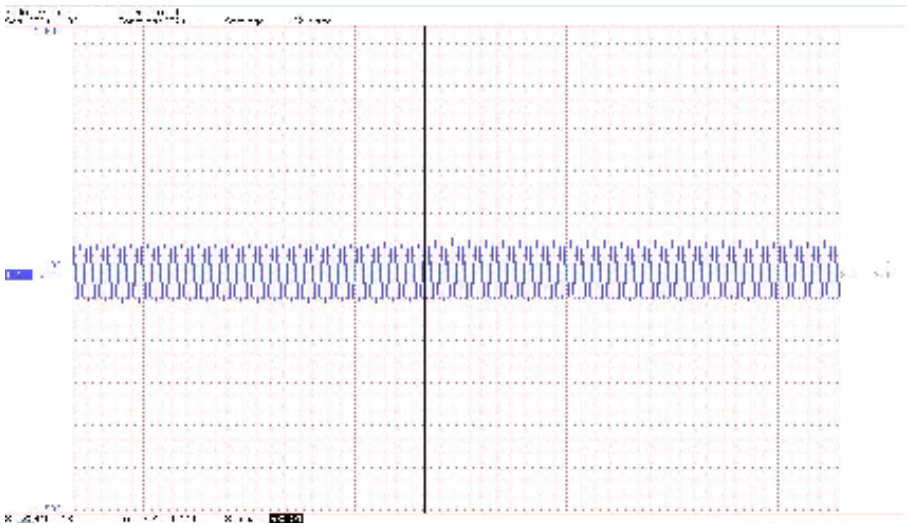
This method is identical to method one except in the placement of the ground and reference electrodes.

1. Remove the electrodes located on the mastoids from the electrode cap.
2. Place the electrode corresponding to the left mastoid 5 cm below the left ear and the electrode corresponding to the right mastoid on 5 cm below the right ear. Secure with medical tape if necessary.
3. Run the test sequence as specified previously for Initial Calibration and Initial Parameters.

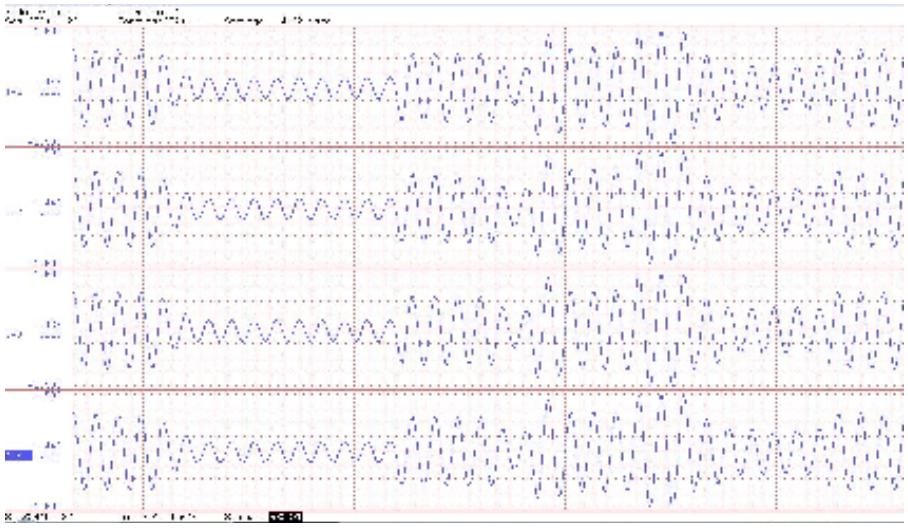
Note:

1. Current medications as well as diagnostic and demographic data will be tracked through an intake form approved by the Drexel University College of Medicine Institutional Review Board.

APPENDIX D: TEST SYSTEM RESULTS



The test system was initially examined using a single electrode to prove that an AC signal could travel through the electrode and be read by a data acquisition program.



Four electrodes may be examined by the DATAQ acquisition system at one time. The AC signal obtained is consistent across each electrode and the electrodes are sensitive to changes in signal amplitude.

APPENDIX E: P300 SPELLING ACCURACY

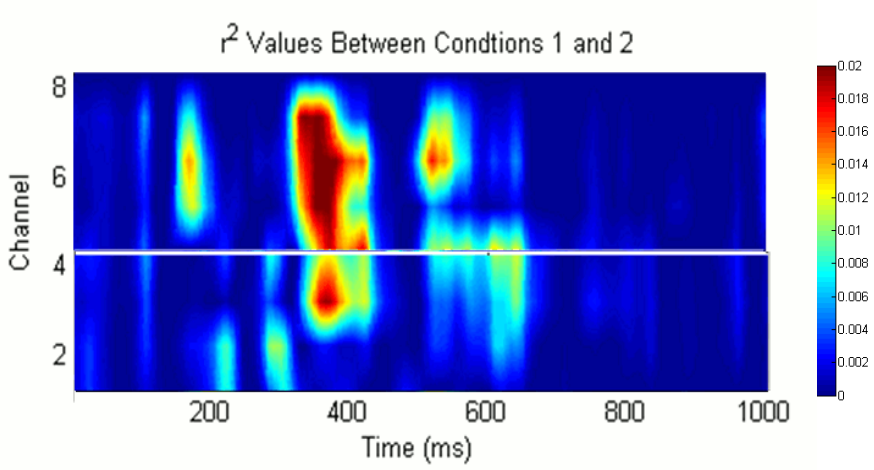
Subject	M/F	Age	Diag	Date of Symptom Onset	Date of Diagnosis	ALSFRS	Percent Correct	Medications
BCI004	M	55	ALS	12/8/2004	2/22/2005	18	93	Rilutek L-Carnitine Neurontin Nexium Chlorazepate Vitamin B Baclofen Avapro Lyrica Tricor
BCI006	M	54	ALS		1/1/1998	27	86	Paxil Zyrtec Clonazepam Tylenol Antara Valium Zanaflex Neurodex
BCI007	F	66	ALS	8/1/2004	4/1/2006	27	71	Hyzaar Zoloft 150 CoQ10 Creatine Robinul Ativan Vitamin B
BCI008	F	57	ALS	8/1/1995	9/23/1999	33	64	Baclofen Tamoxifen Ditropan Tylenol Darvocet

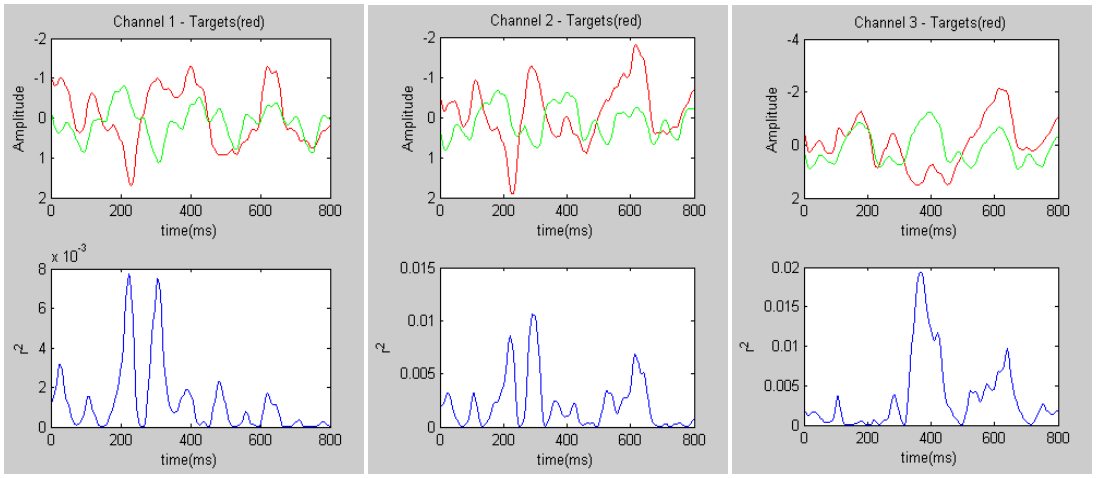
BCI009	M	54	ALS	10/24/2007	1/1/2009	1	100	Albuterol Acetylcysteine Lexapro Vitamin D Ursodiol Neurontin Miralex KCl Feosol, CoQ10 Ultram Indocin Omeprazole Dulcolax Ambien
BCI011	F	48	ALS	8/1/2005	4/24/2007	34	100	Rilutek
BCI012	M	50	ALS	3/1/2005	2/1/2006	1	79	Rilutek Elavil Sudafed Ativan Tylenol Naprosyn Fentanyl Aspirin Nasonex Atrovent Duoneb Centrum Reglan Pulmicort Robitussin Novolog Insulin Lexapro Flexeril Zegerid
BCI013	M	38	ALS		3/25/2005	11	100	Klonopin Baclofen Zyrtec Scopalamine Guaifenecin Restaid Rilutek Arimoclomol Lithium
BCI001	F	43	Control	NA	NA	NA	100	
BCI002	M	24	Control	NA	NA	NA	100	
BCI003	M	22	Control	NA	NA	NA	86	
BCI014	M	23	Control	NA	NA	NA	100	

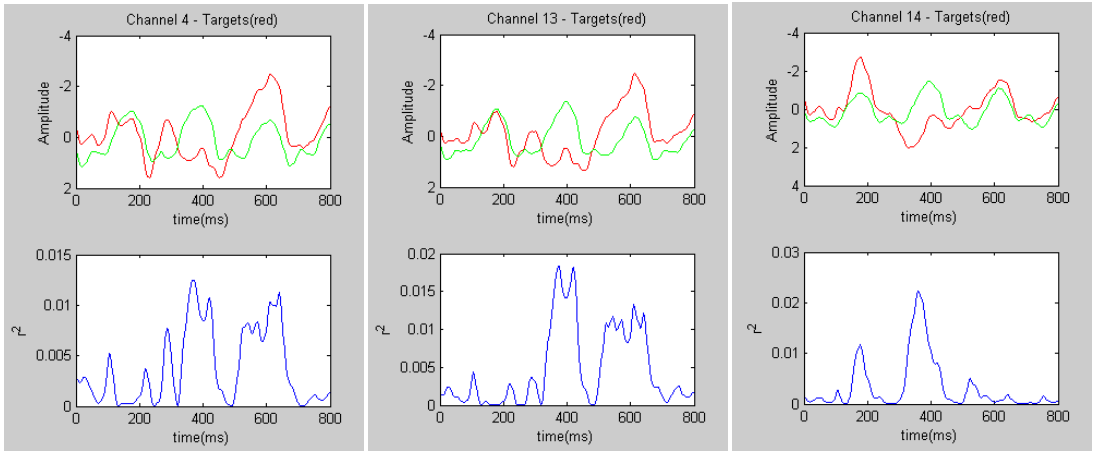
APPENDIX F: ANALYSIS OF THE P300 WAVEFORM BY SUBJECT

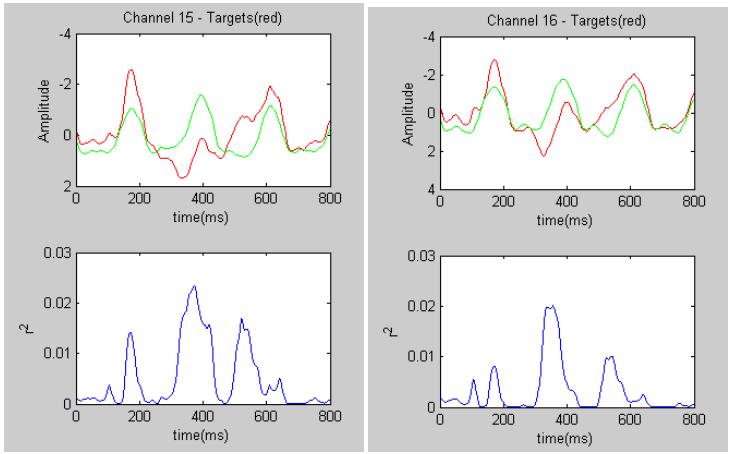
HEALTHY CONTROLS

BCI002

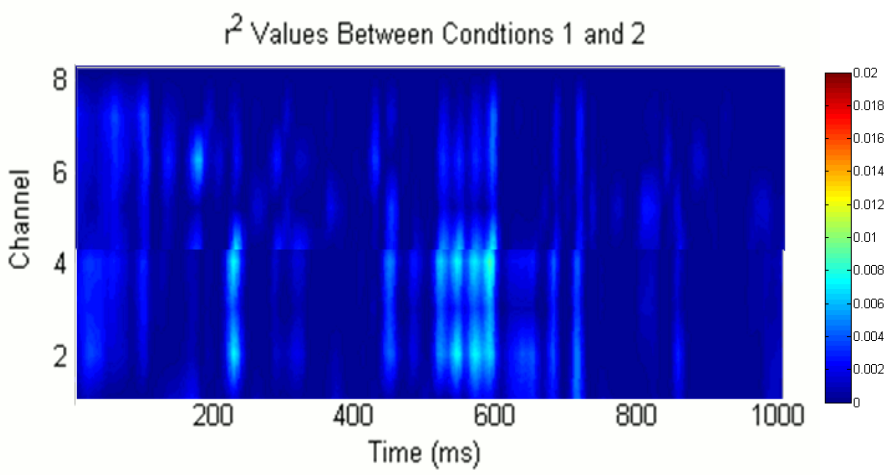


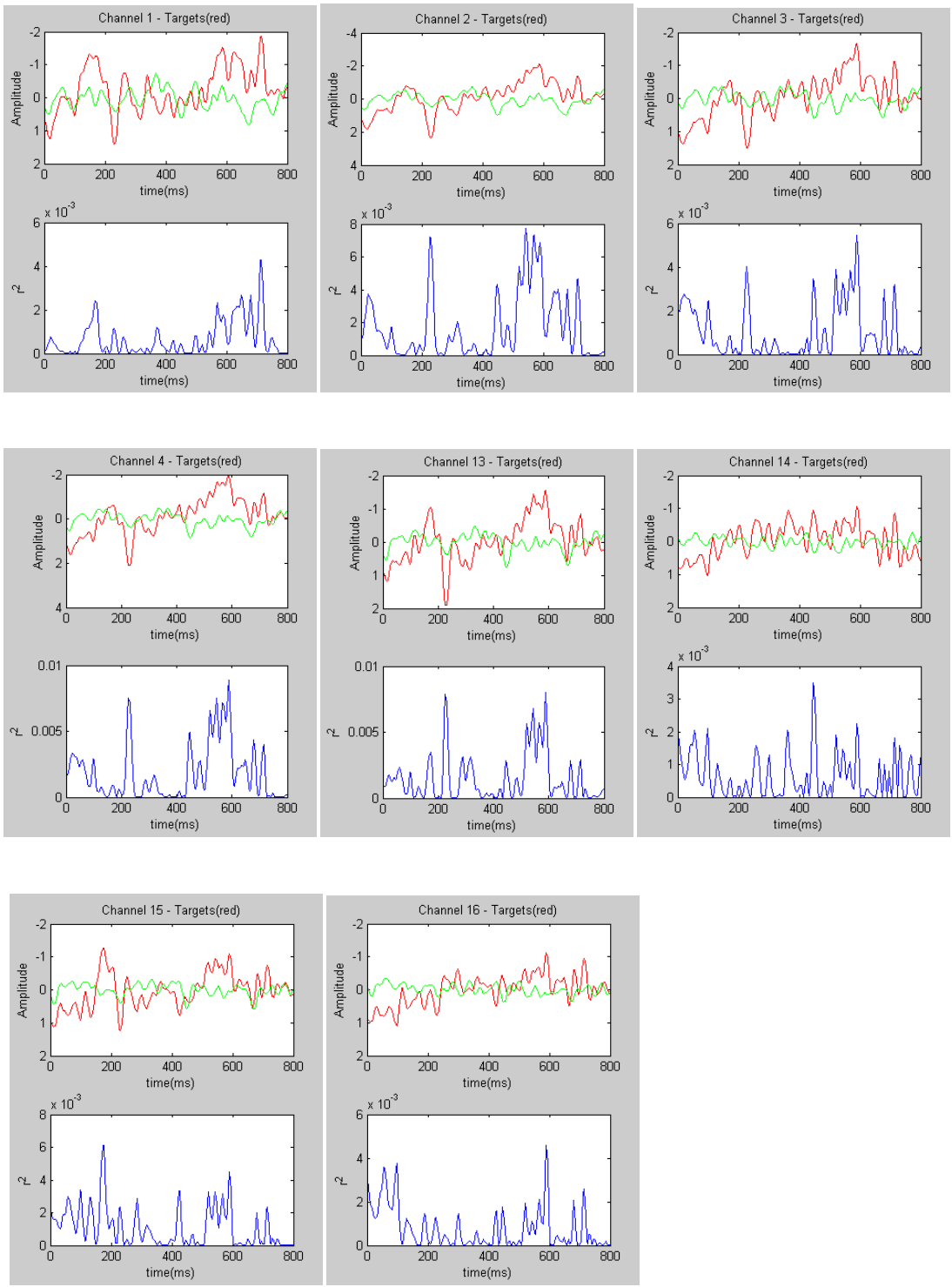



Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Amplitude
time(ms)
r2

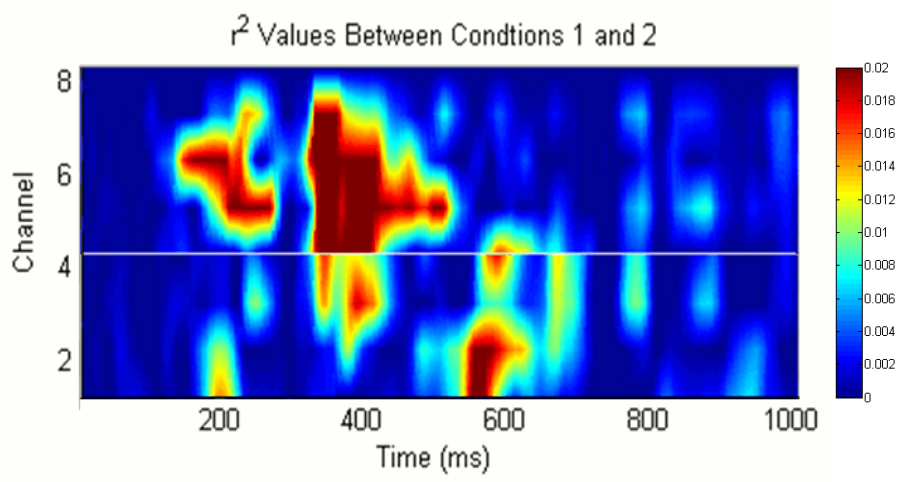

Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
time(ms)
r2

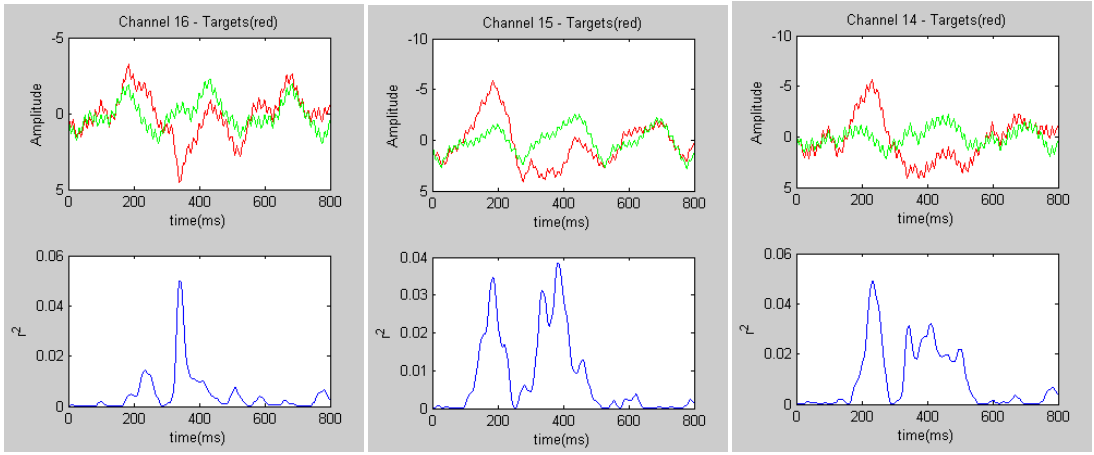
BCI003

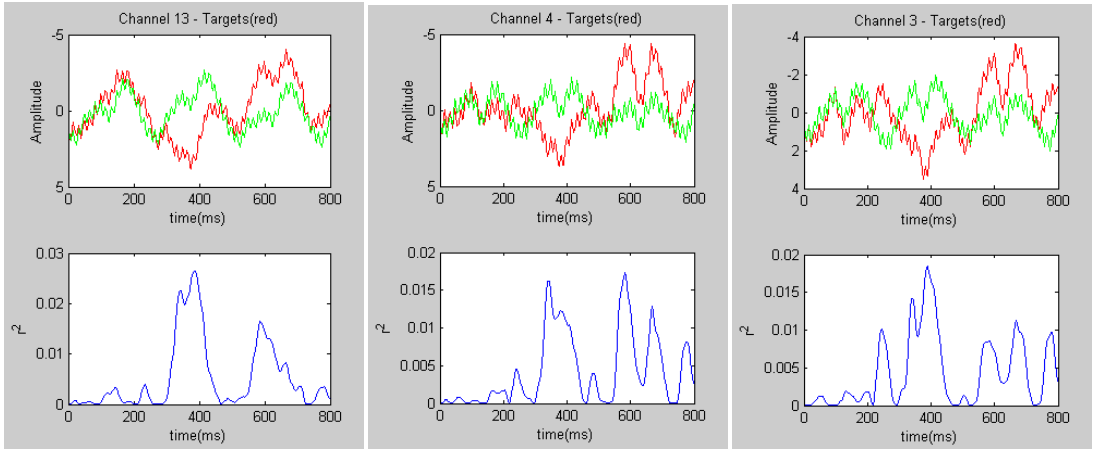

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

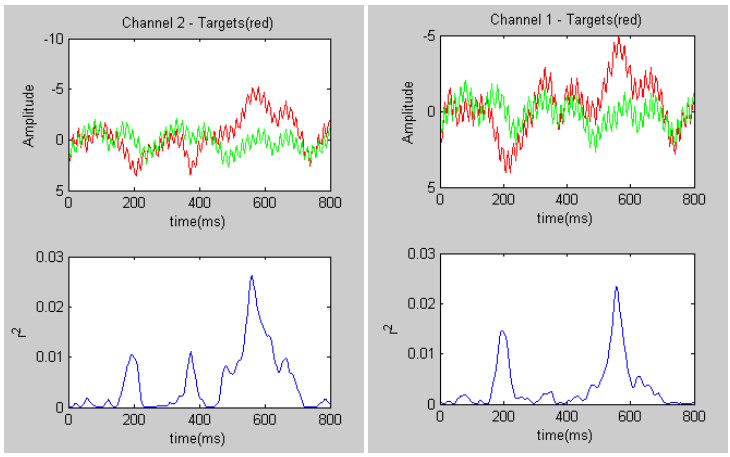

Channel 1 - Targets(red)
Channel 2 - Targets(red)
Channel 3 - Targets(red)
Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
r2
time(ms)
x 10^-3

BCI014


r2 Values Between Condtions 1 and 2
Channel
Time (ms)

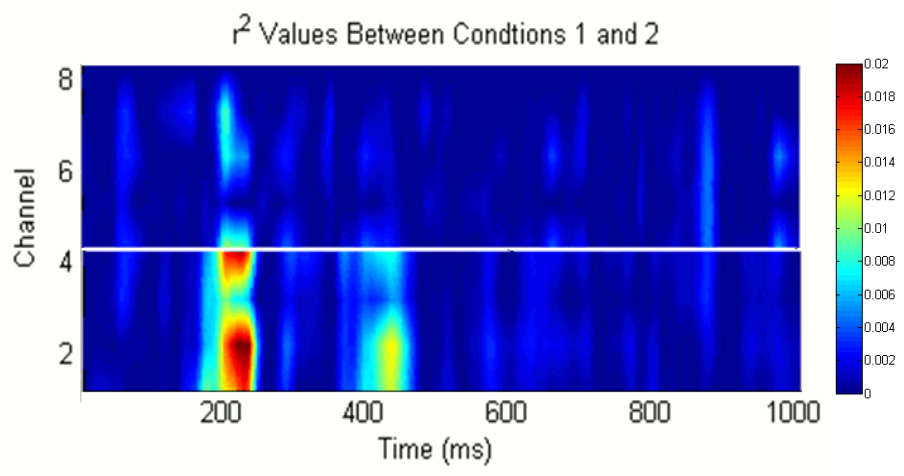

Channel 16 - Targets(red)
Channel 15 - Targets(red)
Channel 14 - Targets(red)
Amplitude
r2
time(ms)

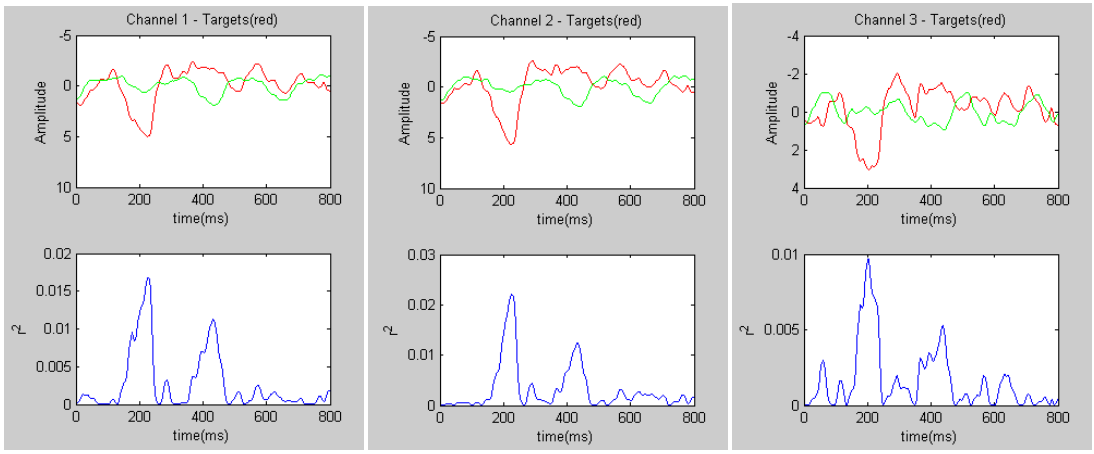

Channel 13 - Targets(red)
Channel 4 - Targets(red)
Channel 3 - Targets(red)
Amplitude
r2
time(ms)

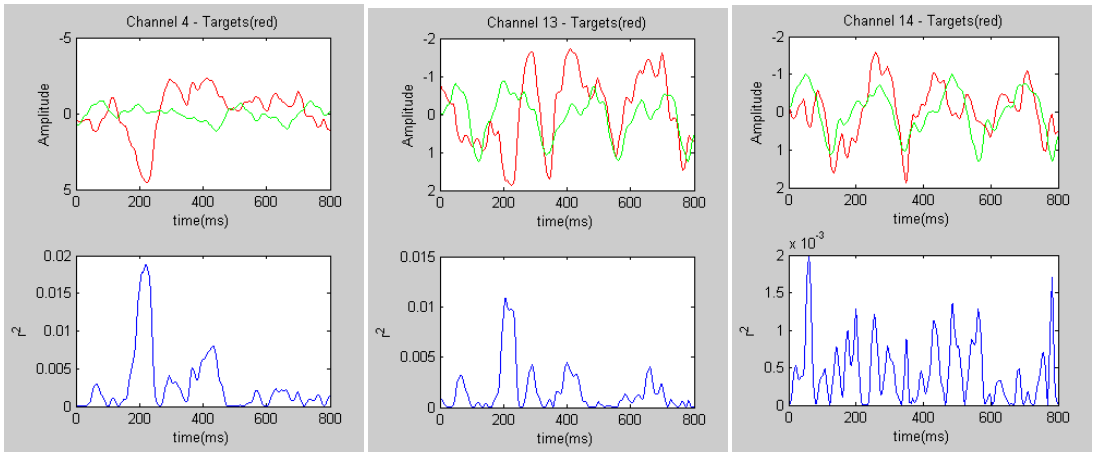

Channel 2 - Targets(red)
Amplitude
time(ms)
r2
time(ms)
Channel 1 - Targets(red)
Amplitude
time(ms)
r2
time(ms)

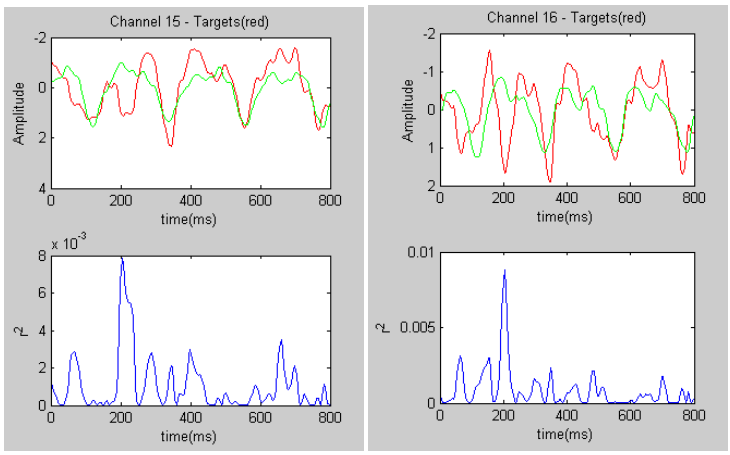
INDIVIDUALS WITH ALS

BCI004

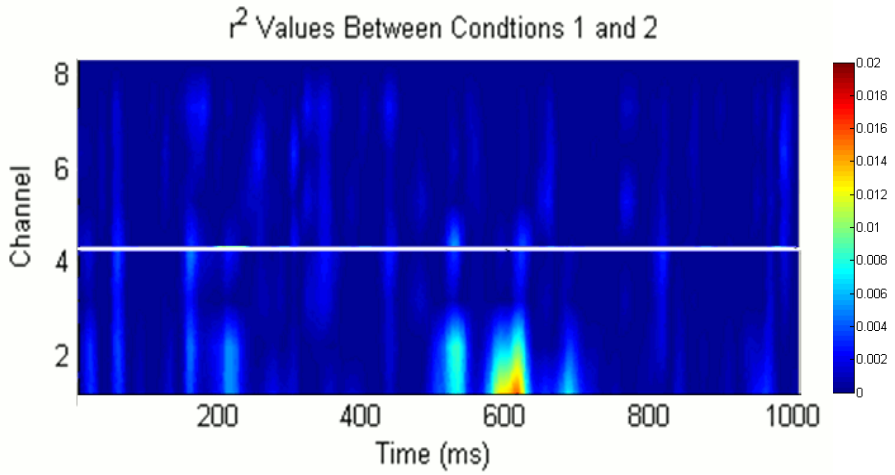


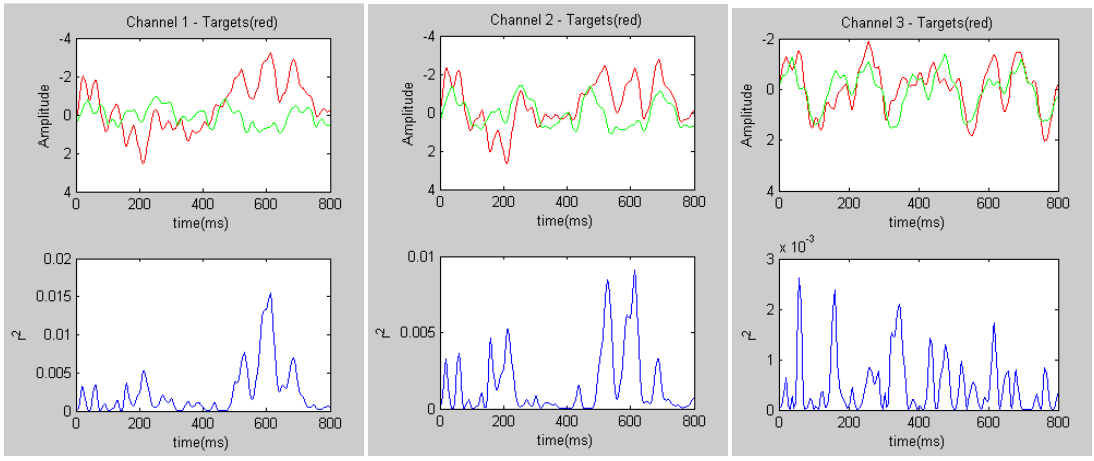


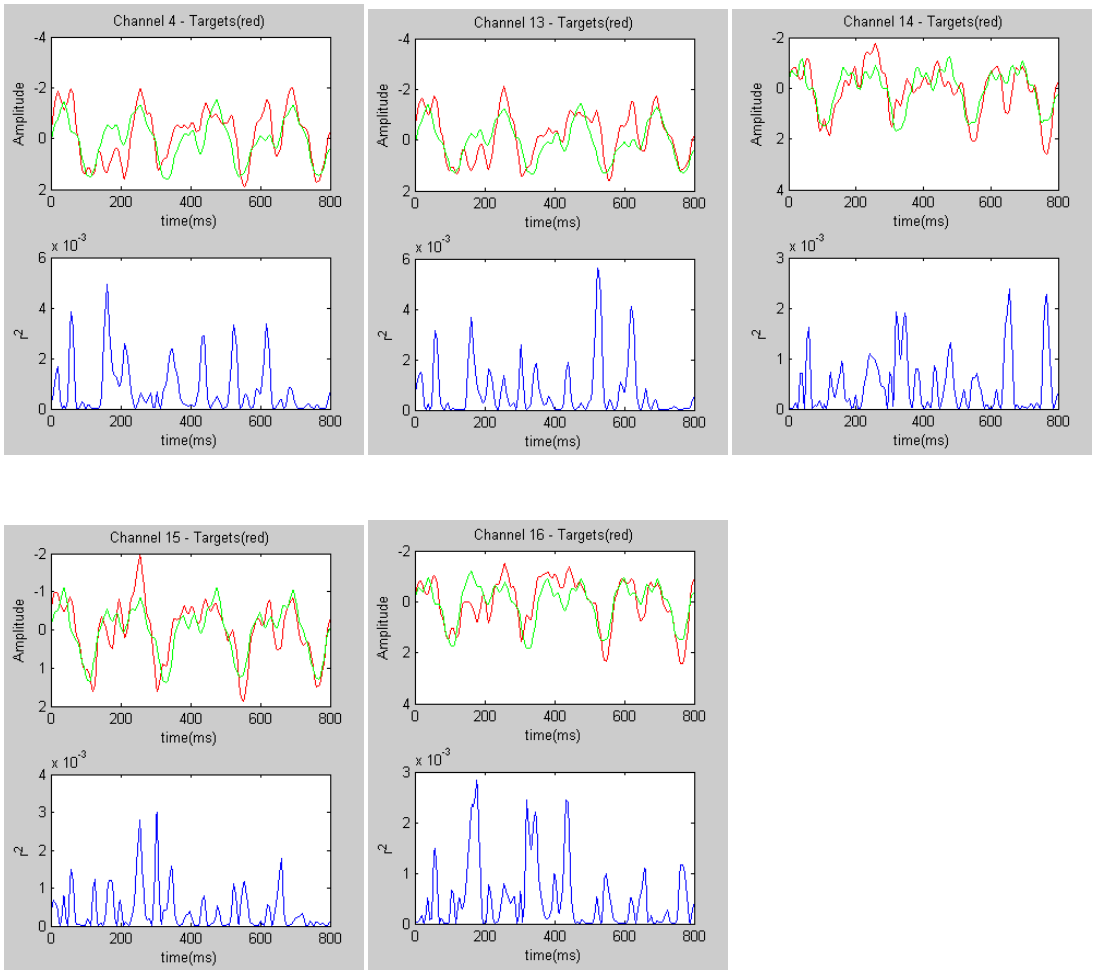



Channel 15 - Targets(red)
Amplitude
time(ms)
r2
x 10-3
Channel 16 - Targets(red)
Amplitude
time(ms)
r2
0.01
0.005

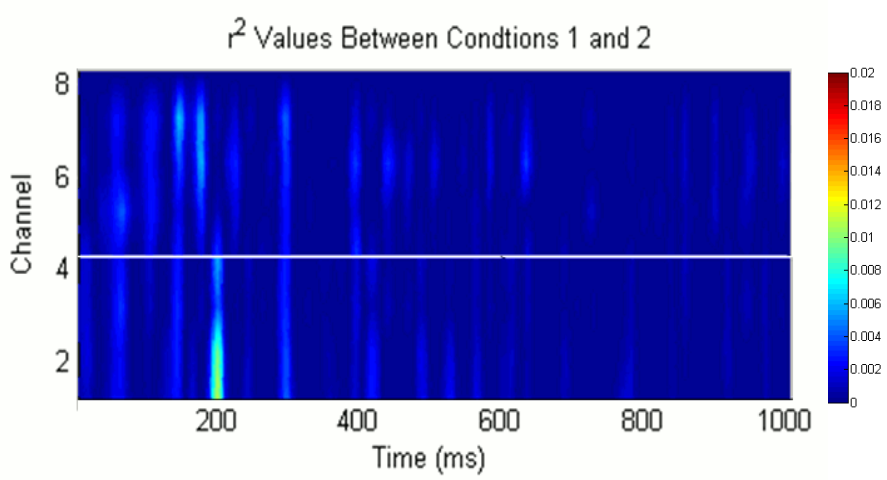
BCI006

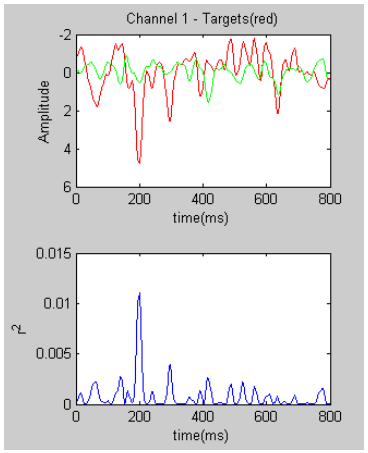

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

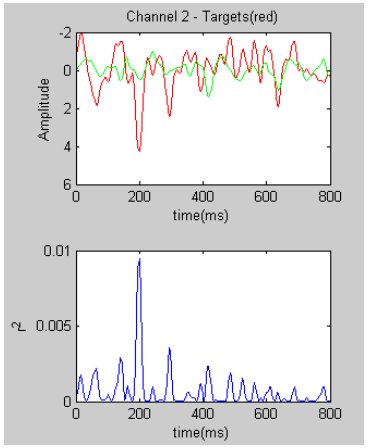

Channel 1 - Targets(red)
Amplitude
time(ms)
r2
Channel 2 - Targets(red)
Amplitude
time(ms)
r2
Channel 3 - Targets(red)
Amplitude
time(ms)
r2
x 10-3

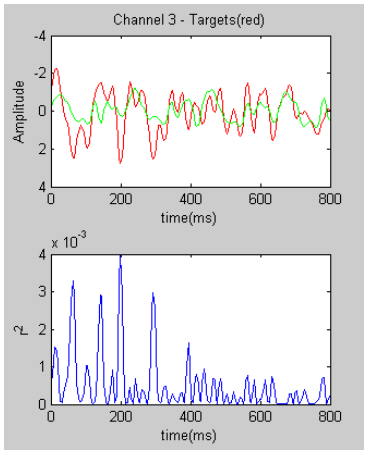

Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
time(ms)
r2
x 10-3

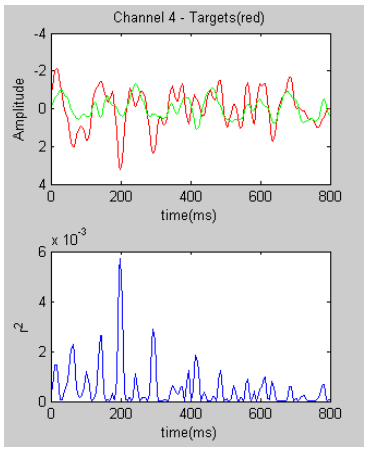
BCI007

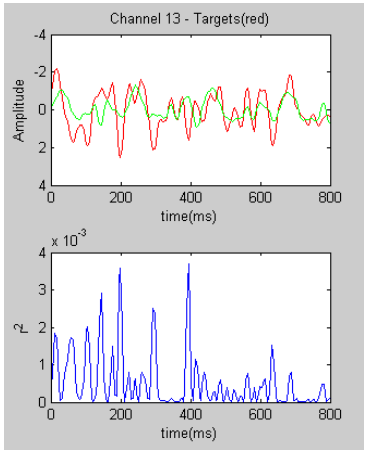

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

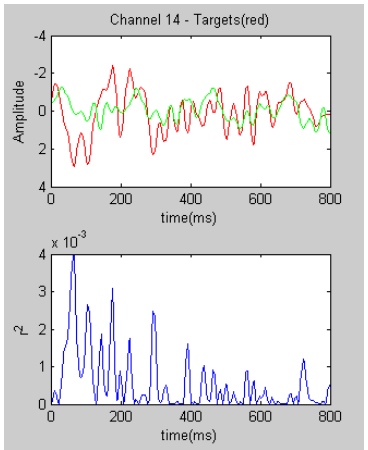

Channel 1 - Targets(red)
Amplitude
time(ms)
r^2
time(ms)

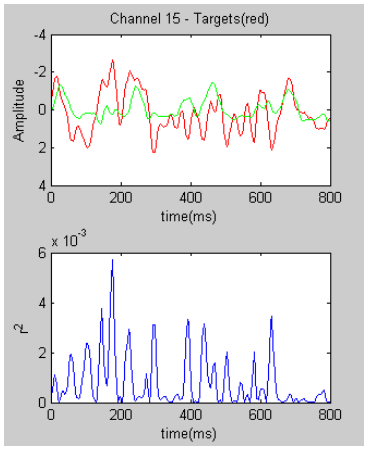

Channel 2 - Targets(red)
Amplitude
time(ms)
r^2
time(ms)

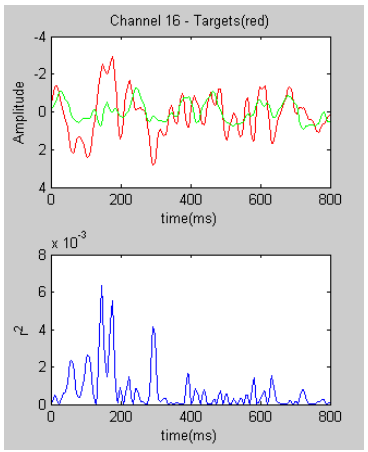

Channel 3 - Targets(red)
Amplitude
time(ms)
x 10^-3
r^2
time(ms)


Channel 4 - Targets(red)
Amplitude
time(ms)
x 10^-3
r^2
time(ms)

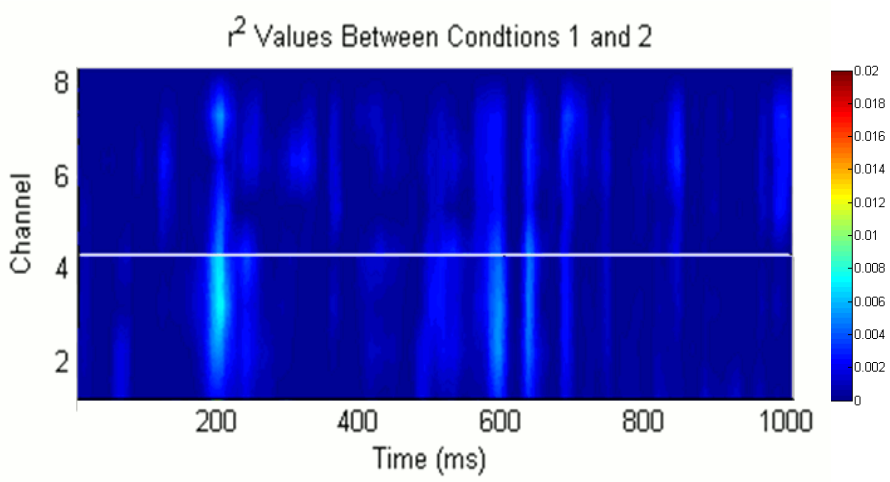

Channel 13 - Targets(red)
Amplitude
time(ms)
x 10^-3
r^2
time(ms)

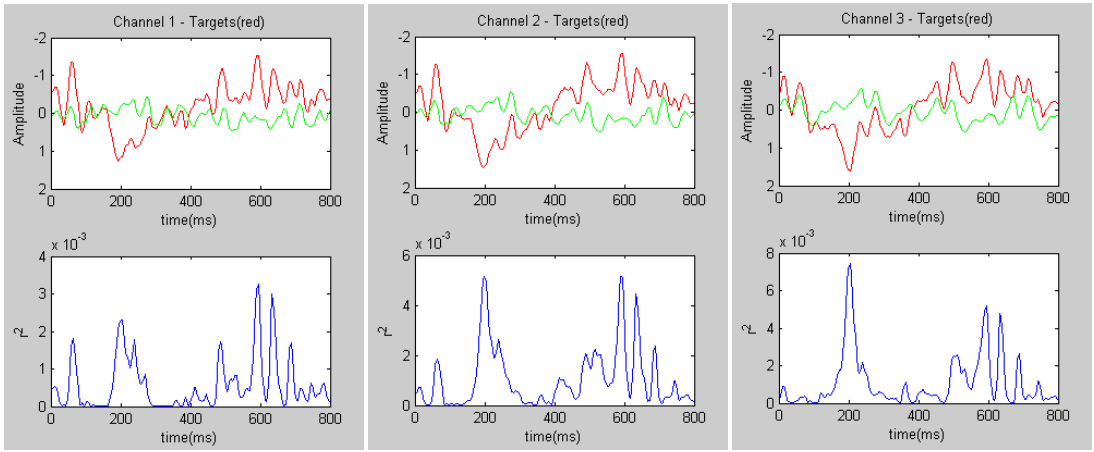

Channel 14 - Targets(red)
Amplitude
time(ms)
x 10^-3
r^2
time(ms)

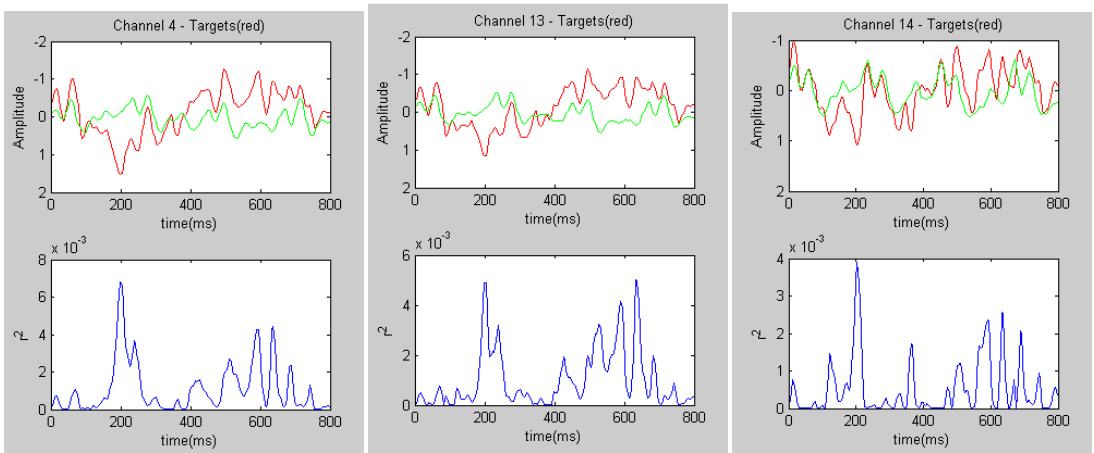

Channel 15 - Targets(red)
Amplitude
time(ms)
x 10^-3
r^2
time(ms)

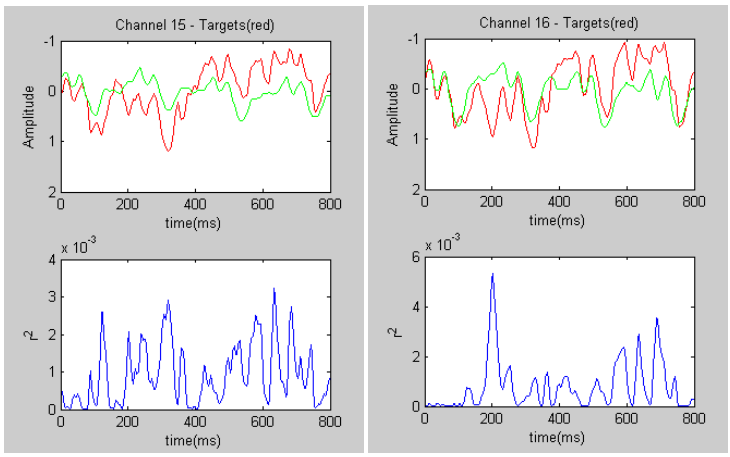

Channel 16 - Targets(red)
Amplitude
time(ms)
x 10^-3
r^2
time(ms)

BCI008

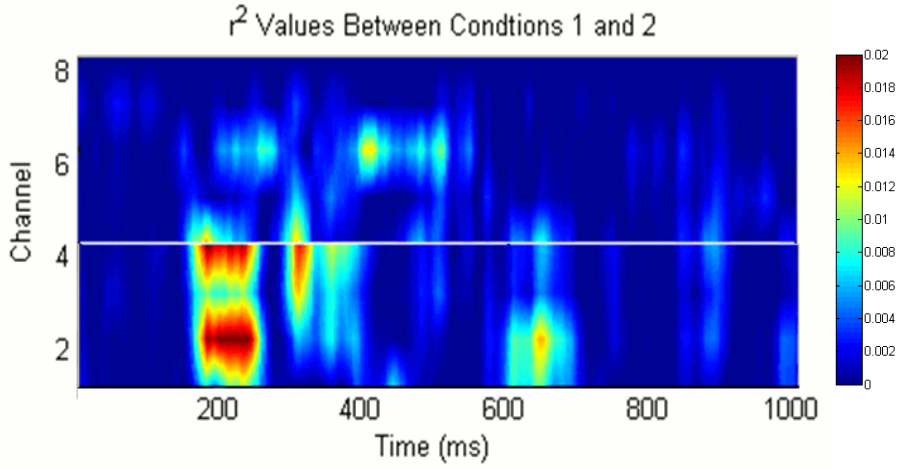

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

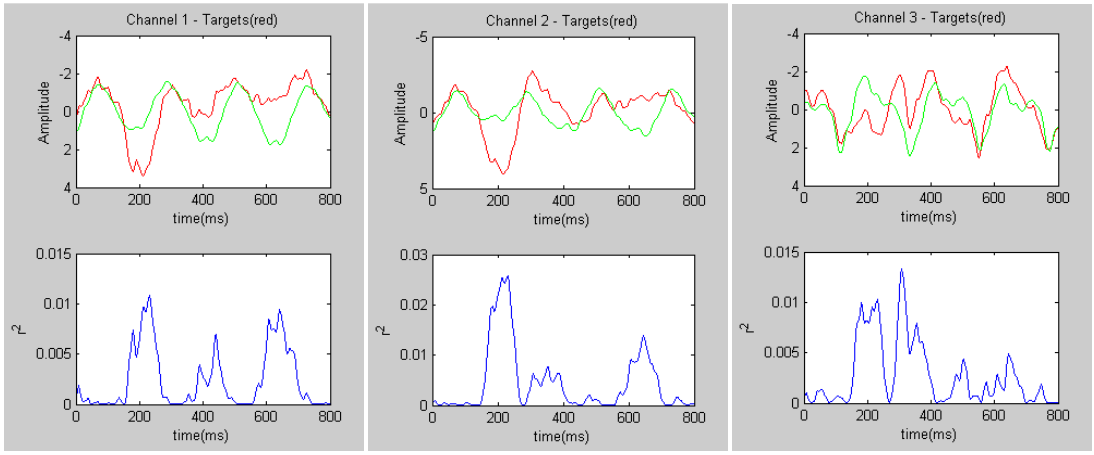

Channel 1 - Targets(red)
Channel 2 - Targets(red)
Channel 3 - Targets(red)
Amplitude
r2
time(ms)

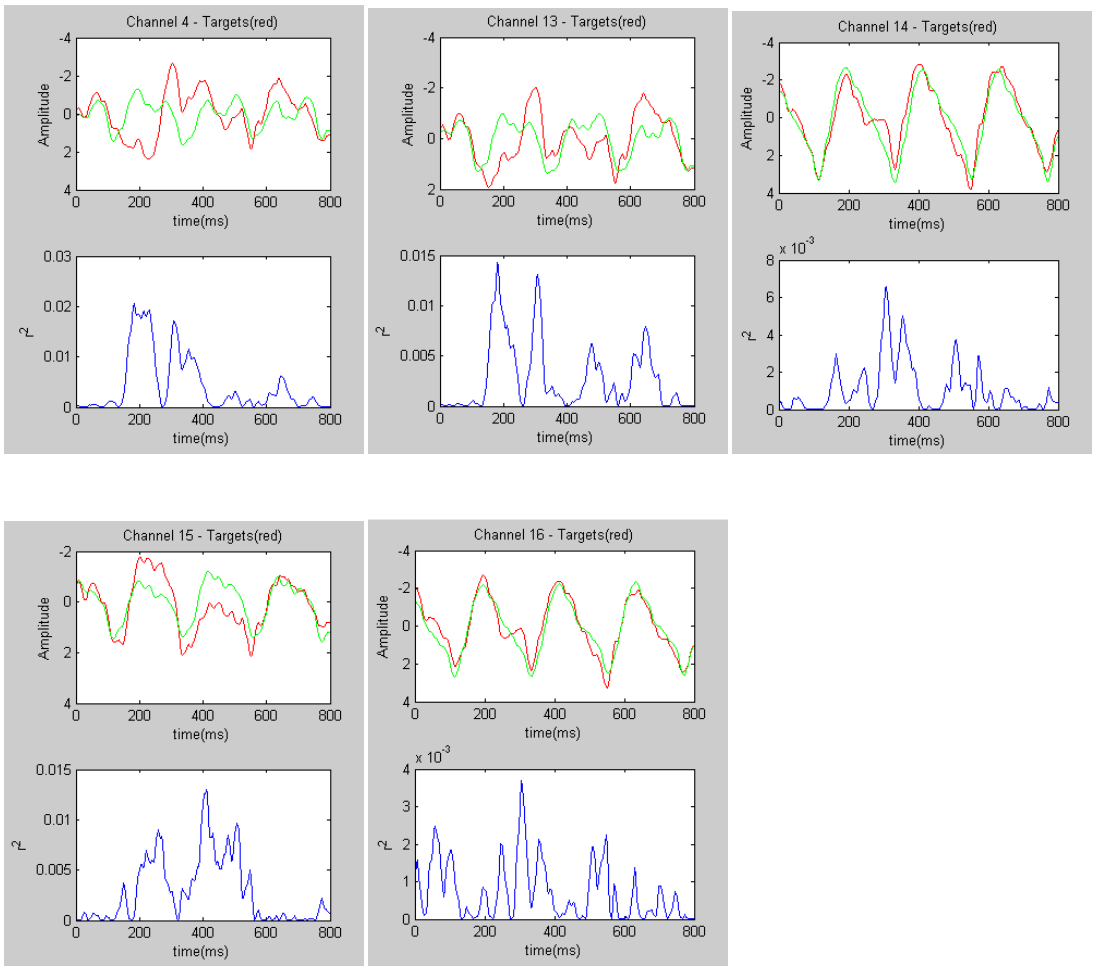

Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Amplitude
r2
time(ms)


Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
time(ms)
r2
x 10-3

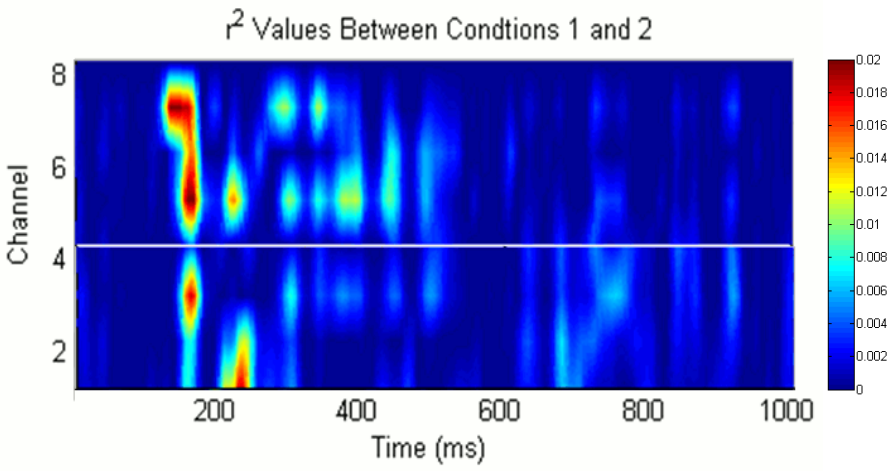
BCI009

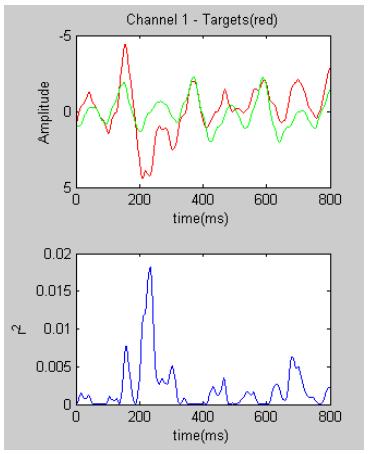

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

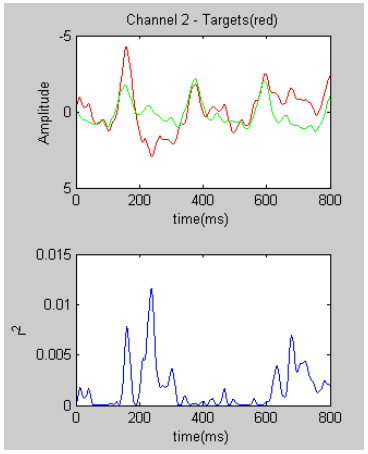

Channel 1 - Targets(red)
Channel 2 - Targets(red)
Channel 3 - Targets(red)
Amplitude
time(ms)
r2

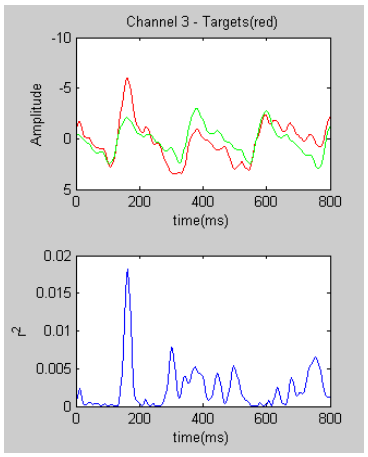

Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
r2
time(ms)
x 10-3

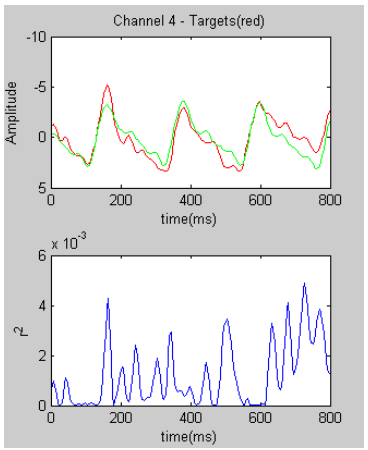
BCI011

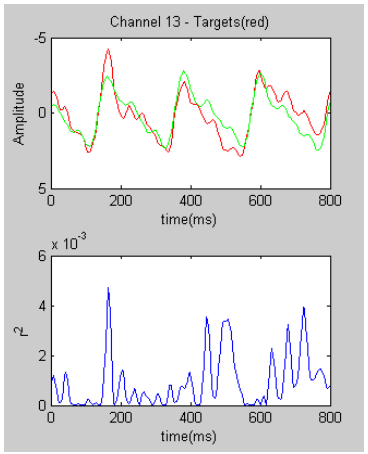

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

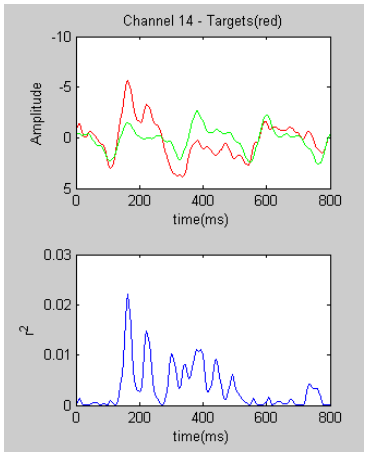

Channel 1 - Targets(red)
Amplitude
time(ms)
r2
time(ms)

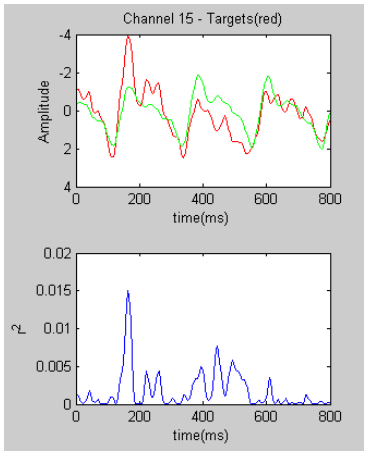

Channel 2 - Targets(red)
Amplitude
time(ms)
r2
time(ms)

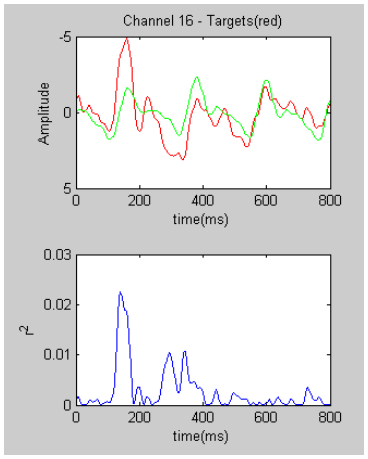

Channel 3 - Targets(red)
Amplitude
time(ms)
r2
time(ms)


Channel 4 - Targets(red)
Amplitude
time(ms)
x 10-3
r2
time(ms)

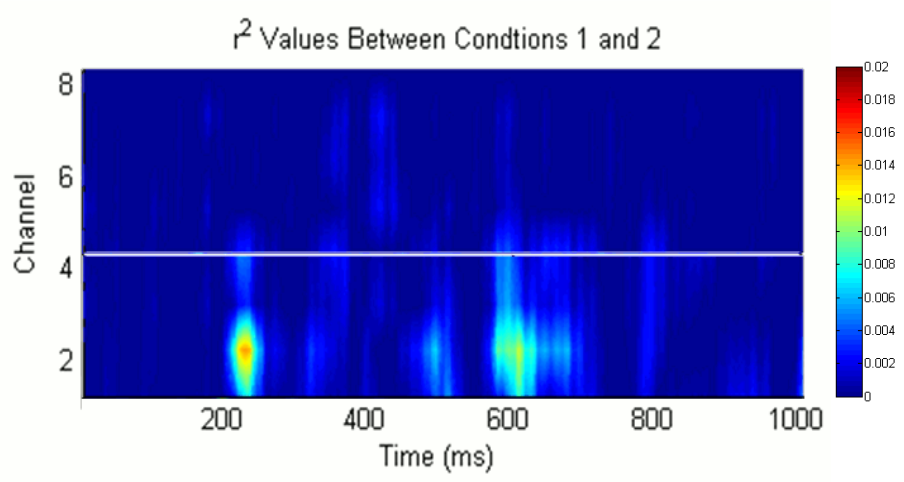

Channel 13 - Targets(red)
Amplitude
time(ms)
x 10-3
r2
time(ms)

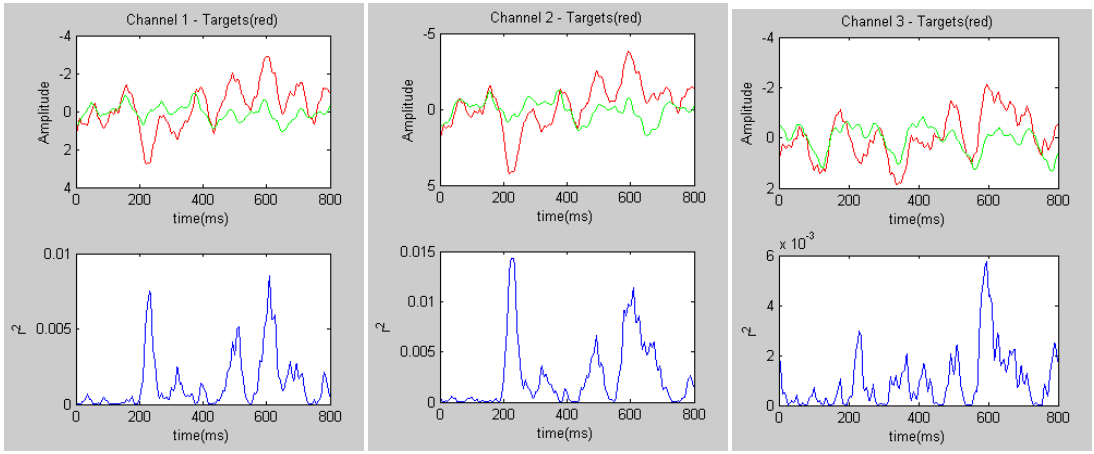

Channel 14 - Targets(red)
Amplitude
time(ms)
r2
time(ms)

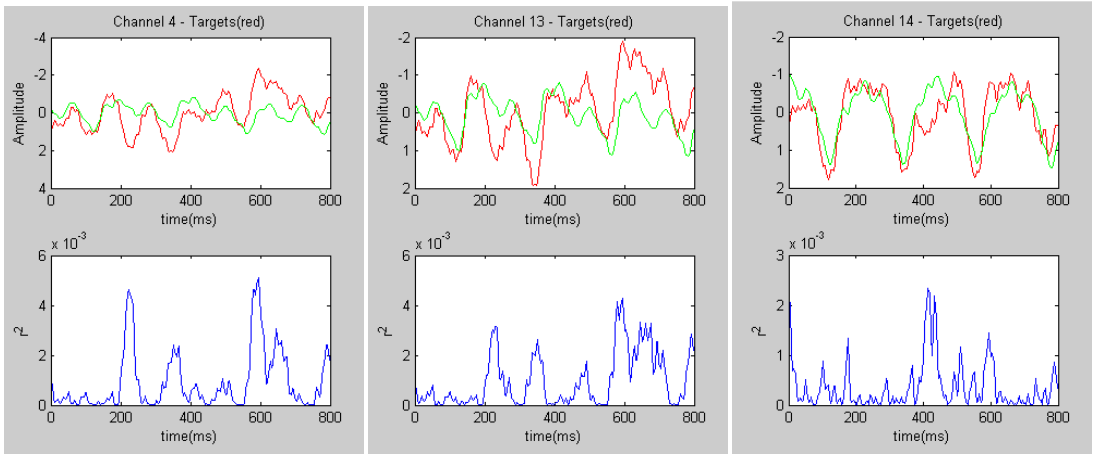

Channel 15 - Targets(red)
Amplitude
time(ms)
r2
time(ms)

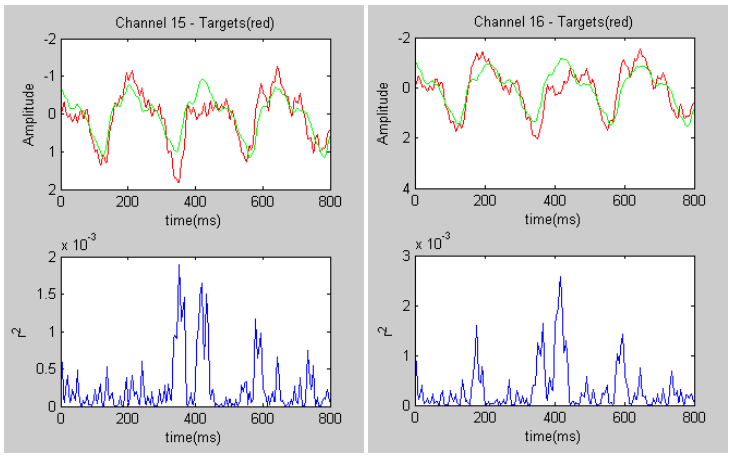

Channel 16 - Targets(red)
Amplitude
time(ms)
r2
time(ms)

BCI012

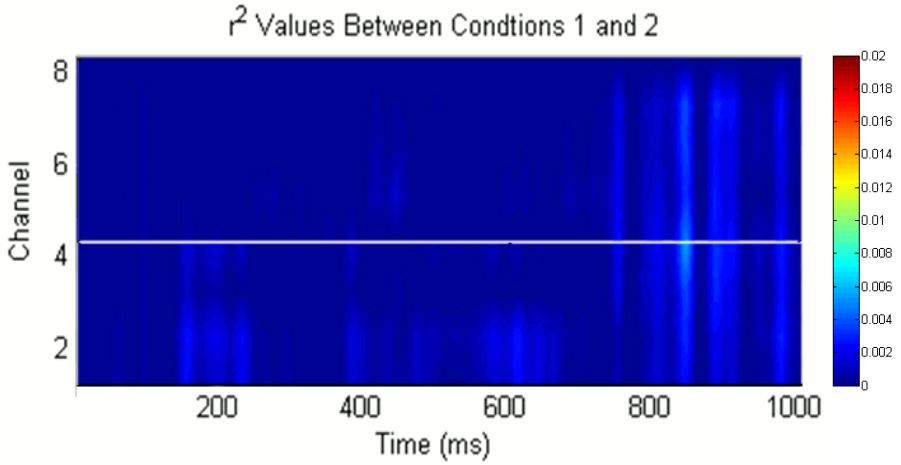

r2 Values Between Condtions 1 and 2
Channel
Time (ms)

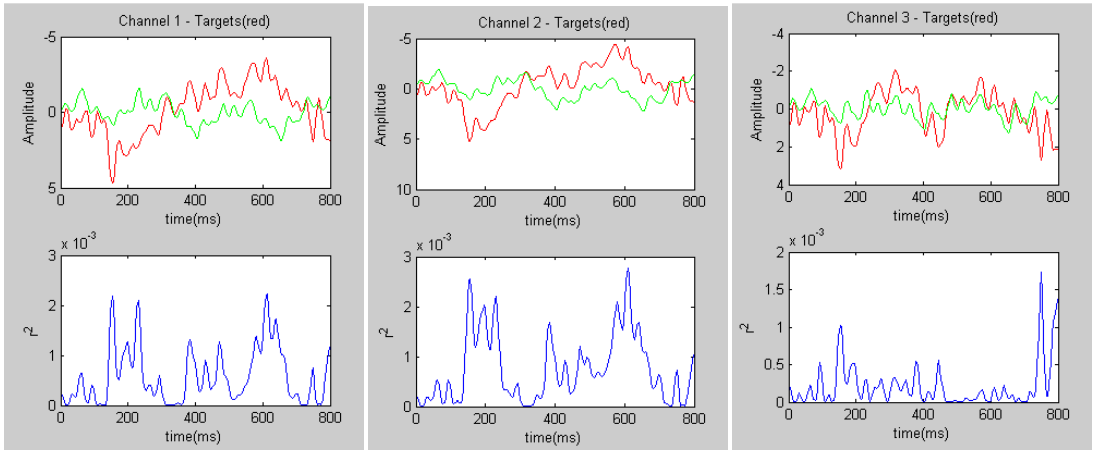

Channel 1 - Targets(red)
Channel 2 - Targets(red)
Channel 3 - Targets(red)
Amplitude
r2
time(ms)

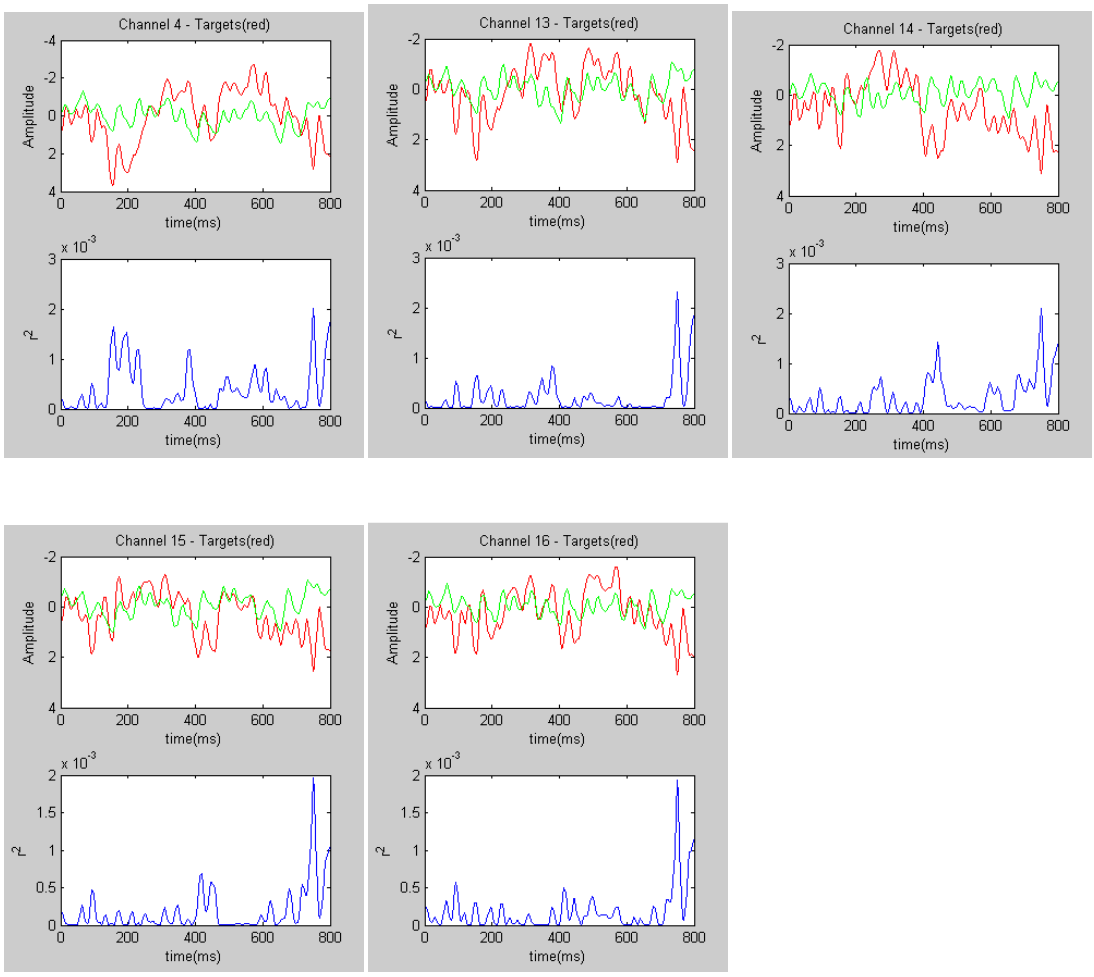

Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Amplitude
r2
time(ms)


Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
time(ms)
r2
x 10-3

BCI013


r2 Values Between Condtions 1 and 2
Channel
Time (ms)


Channel 1 - Targets(red)
Channel 2 - Targets(red)
Channel 3 - Targets(red)
Amplitude
time(ms)
r2
x 10-3


Channel 4 - Targets(red)
Channel 13 - Targets(red)
Channel 14 - Targets(red)
Channel 15 - Targets(red)
Channel 16 - Targets(red)
Amplitude
r^2
time(ms)
x 10^-3

APPENDIX G: PEAK VALUES BY SUBJECT AND CHANNEL

P300 Speller

Subject	Disease	Peak Amplitude				Peak r^2		
		Ch	Time (ms)	Amp (mv)	r^2	Time (ms)	Amp (mv)	r^2
BCI001	Control	1	207.0	2.611	0.010990	527.3	-2.388	0.011880
		2	203.1	2.573	0.015770	515.6	-2.737	0.020800
		3	312.5	2.189	0.001589	156.3	-3.855	0.015940
		4	750.0	1.479	0.000407	515.6	-1.220	0.012740
		5	101.6	1.387	0.000032	515.6	-0.846	0.010810
		6	308.6	2.957	0.008276	183.6	-5.036	0.068610
		7	316.4	2.028	0.003564	214.8	-2.511	0.027580
		8	312.5	2.479	0.005029	160.2	-3.763	0.022860
BCI002	Control	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	230.5	1.691	0.006792	304.7	-1.011	0.007507
		2	226.6	1.901	0.008096	289.1	-1.261	0.010600
		3	359.4	1.517	0.018620	367.2	1.462	0.019380
		4	230.5	1.584	0.002225	371.1	0.829	0.012490
		5	453.1	1.352	0.002304	375.0	0.951	0.018380
		6	328.1	2.036	0.010880	359.4	1.726	0.022250
		7	332.0	1.690	0.016110	371.1	0.830	0.023420
		8	328.1	2.242	0.016960	355.5	1.224	0.020160
BCI003	Control	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	230.5	1.404	0.001149	710.9	-1.853	0.004282
		2	230.5	2.353	0.007140	543.0	-1.723	0.007727
		3	226.6	1.502	0.004030	589.8	-1.659	0.005453
		4	230.5	2.113	0.007197	589.8	-1.994	0.008857
		5	226.6	1.906	0.007895	589.8	-1.567	0.008034
		6	97.7	1.031	0.002096	445.3	-0.942	0.003481
		7	230.5	1.225	0.002328	175.8	-1.280	0.006139
		8	97.7	1.099	0.003774	589.8	-1.123	0.004585
BCI014	Control	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	222.7	4.045	0.006108	554.7	-3.502	0.023370
		2	207.0	3.513	0.009257	558.6	-4.038	0.026110
		3	375.0	3.520	0.014470	390.6	3.336	0.018450
		4	375.0	3.713	0.012140	582.0	-4.418	0.017270
		5	375.0	3.798	0.024730	386.7	3.225	0.026410

		6	375.0	4.098	0.021930	234.4	-5.267	0.048950
		7	277.3	4.060	0.005900	382.8	3.092	0.038470
		8	339.8	4.536	0.049730	339.8	4.536	0.049730
BCI004	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	226.6	5.016	0.016790	226.6	5.016	0.016790
		2	226.6	5.687	0.022150	226.6	5.687	0.022150
		3	203.1	3.044	0.009666	203.1	3.044	0.009666
		4	222.7	4.548	0.018830	222.7	4.548	0.018830
		5	226.6	1.874	0.009767	203.1	1.715	0.010880
		6	347.7	1.885	0.000882	58.6	0.369	0.001989
		7	343.8	2.333	0.002143	203.1	1.098	0.007837
		8	347.7	1.913	0.002353	203.1	1.666	0.008779
BCI006	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	210.9	2.569	0.005293	613.3	-3.236	0.015520
		2	210.9	2.669	0.005194	613.3	-2.314	0.009101
		3	761.7	2.018	0.000843	58.6	-1.495	0.002620
		4	554.7	1.911	0.000524	160.2	1.347	0.004955
		5	554.7	1.575	0.000301	523.4	-1.075	0.005617
		6	765.6	2.614	0.002264	656.3	0.765	0.002389
		7	550.8	1.880	0.001149	304.7	1.626	0.003010
		8	761.7	2.409	0.001174	175.8	0.772	0.002834
BCI007	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	199.2	4.747	0.011010	199.2	4.747	0.011010
		2	199.2	4.278	0.009493	199.2	4.278	0.009493
		3	199.2	2.749	0.003983	199.2	2.749	0.003983
		4	199.2	3.210	0.005728	199.2	3.210	0.005728
		5	199.2	2.525	0.003570	394.5	1.603	0.003687
		6	66.4	2.954	0.003970	62.5	2.843	0.003979
		7	293.0	2.244	0.003103	175.8	-2.643	0.005724
		8	293.0	2.830	0.004154	144.5	-2.437	0.006363
BCI008	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	191.4	1.252	0.002050	593.8	-1.521	0.003253
		2	195.3	1.462	0.005015	199.2	1.440	0.005169
		3	203.1	1.598	0.007460	203.1	1.598	0.007460
		4	199.2	1.527	0.006789	199.2	1.527	0.006789
		5	199.2	1.160	0.004909	632.8	-0.929	0.005035
		6	203.1	1.086	0.003903	203.1	1.086	0.003903
		7	320.3	1.201	0.002927	632.8	-0.795	0.003238
		8	324.2	1.169	0.001101	203.1	0.954	0.005341
BCI009	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	210.9	3.420	0.009678	230.5	2.781	0.010850

		2	214.8	4.052	0.025360	230.5	3.822	0.025710
		3	550.8	2.555	0.000478	308.6	-1.637	0.013320
		4	230.5	2.395	0.019300	183.6	1.727	0.020550
		5	152.3	1.932	0.005015	179.7	1.390	0.014330
		6	546.9	3.823	0.001279	308.6	0.341	0.006564
		7	550.8	2.152	0.004380	410.2	0.363	0.012990
		8	550.8	3.309	0.001942	304.7	0.112	0.003695
BCI011	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	210.9	4.368	0.011780	234.4	4.200	0.018220
		2	238.3	2.934	0.011590	238.3	2.934	0.011590
		3	308.6	3.487	0.006419	164.1	-5.983	0.018210
		4	539.1	3.378	0.000506	726.6	-0.008	0.004874
		5	543.0	2.842	0.000651	164.1	-4.260	0.004725
		6	335.9	3.851	0.006321	164.1	-5.636	0.022140
		7	339.8	2.462	0.001164	164.1	-3.940	0.015070
		8	335.9	3.135	0.008164	140.6	-3.793	0.022520
BCI012	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	222.7	2.748	0.005959	609.4	-2.807	0.008537
		2	218.8	4.225	0.012760	230.5	4.098	0.014290
		3	335.9	1.860	0.001197	593.8	-2.101	0.005780
		4	347.7	2.082	0.002124	593.8	-2.346	0.005111
		5	347.7	1.938	0.002380	593.8	-1.906	0.004276
		6	117.2	1.779	0.000401	414.1	0.527	0.002344
		7	351.6	1.814	0.001885	351.6	1.814	0.001885
		8	351.6	2.057	0.001252	418.0	0.214	0.002569
BCI013	ALS	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	152.3	4.673	0.002188	613.3	-3.446	0.002225
		2	156.3	5.225	0.002556	609.4	-4.145	0.002777
		3	152.3	3.182	0.001017	750.0	2.698	0.001729
		4	152.3	3.656	0.001539	750.0	2.836	0.002013
		5	750.0	2.908	0.002323	750.0	2.908	0.002323
		6	750.0	3.128	0.002095	750.0	3.128	0.002095
		7	750.0	2.546	0.001968	750.0	2.546	0.001968
		8	750.0	2.699	0.001933	750.0	2.699	0.001933

Optimization of Ground and Reference Electrode Placement

Subject	Loc	Peak Amplitude				Peak r^2		
		Ch	Time (ms)	Amp (mv)	r^2	Time (ms)	Amp (mv)	r^2
BCI014	1	1	214.8	3.269	0.008760	585.9	-4.983	0.027840
		2	378.9	3.335	0.010870	585.9	-5.620	0.038170
		3	382.8	3.417	0.018910	644.5	-3.913	0.034030
		4	378.9	3.989	0.017310	585.9	-4.758	0.030740
		5	378.9	4.167	0.035160	386.7	3.676	0.038140
		6	382.8	4.210	0.034830	234.4	-4.478	0.042520
		7	382.8	4.760	0.056600	386.7	4.274	0.058870
		8	335.9	3.789	0.042810	339.8	3.543	0.044070
BCI014	2	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	375.0	2.179	0.003862	558.6	-1.999	0.005893
		2	371.1	3.504	0.010800	367.2	3.292	0.010810
		3	335.9	2.294	0.011330	429.7	1.714	0.015520
		4	335.9	3.042	0.016480	339.8	2.993	0.016940
		5	335.9	4.167	0.024780	339.8	3.995	0.025030
		6	339.8	3.331	0.016920	230.5	-6.549	0.050110
		7	335.9	4.856	0.031360	339.8	4.723	0.031990
		8	339.8	3.933	0.027460	339.8	3.933	0.027460
BCI014	3	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	218.8	2.992	0.002221	175.8	1.429	0.004638
		2	371.1	3.060	0.005121	335.9	1.856	0.005452
		3	332.0	3.025	0.009374	335.9	3.003	0.010320
		4	281.3	3.425	0.000827	335.9	3.135	0.010260
		5	281.3	4.890	0.003132	335.9	3.710	0.012720
		6	335.9	4.326	0.013540	339.8	4.160	0.014580
		7	281.3	6.111	0.006309	339.8	4.049	0.015780
		8	335.9	4.206	0.016450	339.8	4.139	0.017450
BCI015	1	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	410.2	2.875	0.007030	707.0	-3.637	0.027730
		2	418.0	1.924	0.004805	707.0	-2.216	0.020330
		3	156.3	1.140	0.002470	371.1	-2.177	0.009135
		4	226.6	1.921	0.005386	652.3	-1.533	0.010420
		5	234.4	2.178	0.010370	378.9	-2.612	0.019000
		6	148.4	0.720	0.001910	371.1	-2.531	0.020580
		7	238.3	0.996	0.003199	375.0	-2.040	0.029880
		8	242.2	1.283	0.002909	429.7	1.058	0.014950
BCI015	2	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	218.8	3.383	0.004589	636.7	-5.093	0.018200

		2	222.7	3.337	0.004610	632.8	-3.847	0.011350
		3	230.5	2.415	0.003180	593.8	-2.491	0.004653
		4	230.5	3.198	0.004990	597.7	-2.902	0.005566
		5	234.4	3.434	0.005969	234.4	3.434	0.005969
		6	785.2	2.756	0.004794	785.2	2.756	0.004794
		7	785.2	2.150	0.003557	441.4	1.561	0.004698
		8	468.8	2.396	0.003053	441.4	1.736	0.004925
BCI012	1	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	214.8	3.991	0.005479	230.5	3.856	0.006180
		2	214.8	4.444	0.008628	214.8	4.444	0.008628
		3	347.7	2.356	0.003620	332.0	2.258	0.003936
		4	214.8	2.302	0.005477	214.8	2.302	0.005477
		5	332.0	2.015	0.003784	246.1	1.897	0.005460
		6	347.7	1.930	0.002108	414.1	0.610	0.002142
		7	332.0	1.997	0.002827	332.0	1.997	0.002827
		8	347.7	2.278	0.003013	347.7	2.278	0.003013
BCI012	2	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	218.8	2.634	0.004489	644.5	-1.173	0.004849
		2	214.8	3.631	0.006310	609.4	-3.064	0.009534
		3	351.6	2.170	0.001130	593.8	-2.229	0.004263
		4	351.6	1.968	0.001258	593.8	-2.508	0.005458
		5	347.7	2.026	0.000610	609.4	-1.967	0.003464
		6	351.6	2.063	0.000616	593.8	-1.360	0.002548
		7	347.7	2.039	0.000487	226.6	-2.406	0.003228
		8	347.7	2.314	0.000349	402.3	0.503	0.002108
BCI012	3	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	242.2	2.403	0.004629	484.4	-3.320	0.006742
		2	242.2	3.271	0.006826	585.9	-3.882	0.008604
		3	343.8	3.085	0.001700	585.9	-2.655	0.005079
		4	343.8	3.082	0.002076	585.9	-3.018	0.006414
		5	343.8	3.541	0.002643	585.9	-2.351	0.004354
		6	343.8	2.808	0.001054	585.9	-1.522	0.002545
		7	343.8	3.502	0.003204	218.8	-3.266	0.005010
		8	343.8	3.576	0.001872	375.0	1.445	0.003119
BCI006	1	Ch	Time	Amp	r^2	Time	Amp	r^2
		1	210.9	2.174	0.004282	628.9	-2.839	0.018760
		2	210.9	2.369	0.005029	628.9	-1.807	0.011330
		3	113.3	1.733	0.000634	636.7	-1.211	0.004235
		4	175.8	1.702	0.005749	175.8	1.702	0.005749
		5	175.8	1.769	0.007764	175.8	1.769	0.007764
		6	113.3	1.883	0.000793	636.7	-1.118	0.003064

		7	117.2	1.559	0.001193	128.9	1.154	0.003996
		8	546.9	1.921	0.000399	132.8	1.086	0.005376
		Ch	Time	Amp	r^2	Time	Amp	r^2
		1	402.3	1.723	0.002028	664.1	-2.566	0.024790
		2	183.6	2.291	0.004982	668.0	-0.436	0.005944
		3	632.8	1.892	0.002855	503.9	1.245	0.009139
BCI006	2	4	632.8	1.839	0.002838	558.6	1.078	0.005402
		5	632.8	1.959	0.002083	503.9	0.622	0.005965
		6	632.8	2.553	0.007126	507.8	1.180	0.011100
		7	632.8	2.114	0.004221	503.9	0.938	0.008693
		8	632.8	2.113	0.004286	503.9	0.961	0.008769
		Ch	Time	Amp	r^2	Time	Amp	r^2
		1	183.6	1.545	0.001161	609.4	-2.764	0.006185
		2	183.6	2.259	0.002133	609.4	-1.895	0.002999
		3	632.8	2.001	0.001390	582.0	1.656	0.003585
BCI006	3	4	183.6	1.889	0.001427	371.1	-1.131	0.003724
		5	632.8	2.016	0.000820	457.0	-2.047	0.002132
		6	632.8	2.765	0.003273	582.0	2.163	0.004943
		7	632.8	2.686	0.003005	582.0	1.982	0.004339
		8	632.8	2.686	0.003067	582.0	1.998	0.004440