Predicting Vigilance Performance Under Transcranial Direct Current Stimulation

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PREDICTING VIGILANCE PERFORMANCE UNDER TRANSCRANIAL DIRECT CURRENT STIMULATION

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Engineering

By

NATHANIEL REESE BRIDGES
B.S., Washington University in St. Louis, 2009

2011
Wright State University
I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Nathaniel Reese Bridges ENTITLED Predicting Vigilance Performance Under Transcranial Direct Current Stimulation BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science in Engineering.

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ABSTRACT

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Predicting Vigilance Performance Under Transcranial Direct Current Stimulation

A brain stimulation technology called transcranial direct current stimulation (tDCS) may potentially mitigate the vigilance decrement. To practically use such technology, however, a model is necessary that indicates vigilance performance, both when stimulation is being applied and not applied. To address this issue, the author developed models capable of predicting vigilance performance in real and control stimulation conditions using previous tDCS-study data. The “all possible combinations” regression method produced over 200 models, later screened to 10. The model with the best average %error (11.49 ± 0.10) used left hemispheric cerebral blood flow velocity (CBFVL) as its sole input term—accounting for 95.7% of the performance variability (linear best-fit slope of 0.8585). When applied to the control stimulation condition, the model had an average %error of 16.76 ± 0.17 and linear best-fit slope of 0.9278. Such results suggest that CBFVL may be useful as a vigilance performance metric during tDCS applications.
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1.0 INTRODUCTION

We use vigilance every day. We use it when we drive our cars home from work or school, when we are attending to potential threats in an unknown environment, or when we are looking for a familiar landmark or friend. It is our ability to maintain focus or sustained attention over long periods of time. Formally, vigilance is defined as an individual’s “state of readiness to respond to rarely and unpredictably occurring signals” (Sarter, Givens, & Bruno, 2001). As discussed in Warm, Parasuraman, and Matthews (2008), vigilance is becoming increasingly important as the role of the worker has shifted from active controllers to supervisors of systems. This shift is driven largely by the advancement of technology that has taken on many repetitive tasks once carried out by human beings. Examples include military surveillance, air traffic control, seaboard navigations, industrial process/quality control, medical screening and inspections, surgery, radioactive material detection and airport baggage inspection (Warm et al., 2008). Even though technology has successfully taken on some traditional human roles the human being must still be involved and make the ultimate important decisions. In this case, as human beings, we can only exercise a high state of vigilance for a finite period of time. That is, we eventually experience what is called a vigilance decrement—a decline in vigilance performance over time. As the reader might imagine, the vigilance decrement can be problematic in scenarios where high vigilance is important (see “Statement of Problem”). This thesis provides a predictive regression model in relation to an intervention that addresses this problem area (see “Purpose of Thesis”).
2.0 STATEMENT OF PROBLEM

The vigilance decrement is problematic because human errors that result from it can be costly. In the military setting in particular, these costs can equal lost lives. An air traffic controller missing a critical signal that leads to planes colliding or an image analyst missing an unknown threat that leaves troops vulnerable in an attack are two examples. In an epoch that has moved away from the methodical nature of the Industrial Age to the data and technologically driven Information Age of the present, potential problems such of these will become more prevalent in the future. In other words, the human ability to interface with increasingly advancing technology and the large amounts of data that comes with it is becoming increasingly important.

As a society—in an effort to optimize performance, we have made much progress in developing means to manage these large amounts of data (e.g. smart phones, social networking sites, software packages) and improve our abilities to interface with these means (e.g. ergonomics and human factors). We have put less focus, however, on improving the human beings that operate these means—particularly the cognitive skill sets required to process increased information amounts. This is why the military has begun investigating technologies like transcranial direct current stimulation (tDCS) that might enhance or mitigate decrements in essential cognitive skill sets such as vigilance.

Efforts at the Air Force Research Laboratory (AFRL) suggest that tDCS can influence vigilance performance (publication in preparation). At this time, however, these effects cannot be predicted. Additionally, it is not known how other factors (e.g. changes in blood flow) might influence these effects. A model, therefore, is necessary to provide some scope of tDCS-vigilance effects and relate the key variables involved. This model
could then be used to drive systems dedicated to optimizing cognitive performance, enable users to design and tailor stimulation paradigms for particular settings, and estimate the effectiveness of tDCS-effects in dynamic environments.

Additionally, metrics that provide real-time vigilance levels, both during tDCS and without tDCS are lacking. Without this sense of an individual’s performance we cannot answer questions concerning when and for how long to provide stimulation. For example, a user might decide that a vigilance performance level of 60% is unacceptably dangerous for a task. To address this issue the user may desire to apply tDCS as the individual’s performance reaches 65% and then stop stimulating once the individual’s performance reaches 80%. Without some knowledge concerning the individual’s performance level, however a user cannot do this. A metric that provides a real-time measure of vigilance performance, therefore is also needed.
3.0 PURPOSE OF THESIS

As discussed, a model that is capable of predicting vigilance performance under tDCS is necessary. To begin addressing this issue, the aim of this thesis was to develop an optimized multiple regression model that is capable of predicting vigilance performance during real and sham stimulation using the metrics gathered in the McKinley Study (see “McKinley Study” section; chapter 9). The regression model will predict the individual task percent accuracy relative to baseline performance value every ten minutes (i.e. task performance divided by baseline performance; equation 1) while undergoing tDCS. Since the model output (VP*) predicts values of an individual’s task performance divided by their baseline, individual vigilance performance can be approximated by multiplying the model output by the individual’s baseline performance (equation 2). The result is a model capable of predicting individual vigilance performance (and hence the vigilance decrement) both during and after stimulation.

\[
\text{Model Output} \equiv VP^* \approx \left( \frac{\text{Performance}}{\text{Baseline}} \right)_{\text{avg}} \times (\text{Baseline Performance})_{\text{Indiv.}} \quad \text{(Equation 1)}
\]

\[
\text{Vigilance Performance}_{\text{Indiv.}} = \left( \frac{\text{Performance}}{\text{Baseline}} \right)_{\text{avg}} \times (\text{Baseline Performance})_{\text{Indiv.}} \quad \text{(Equation 2)}
\]

This thesis then, will address the following questions:

1) How well can the averaged normalized vigilance performance (VP*\text{avg.})—both during and after tDCS, be predicted using the average (across subjects) of any if not all of the following metrics: right and left hemispheric cerebral blood flow velocity (CBFV), regional cerebral oxygen saturation (rSO₂), heart rate (HR) and
the stimulation parameters (e.g. location and polarity) used in the McKinley Study (see chapter 9) ?

2) Which of these metrics (or input variables) are key in predicting VP*<sub>avg</sub> (during and after tDCS) and hence tDCS-vigilance effects for both real <i>and</i> control (anodal and sham respectively) stimulation conditions?

3) How well can VP*<sub>avg</sub> be used to predict vigilance performance (% hits) in individual subjects—both during and after tDCS for both real <i>and</i> control stimulation conditions?
4.0 BACKGROUND

Imagine staring at a screen for hours, waiting for a critical moment that may or may not occur. You do your best to remain focused but as soon as your attention begins to wane that critical moment occurs and you miss it. For WWII submarine operators this scenario was commonplace. They spent long time periods looking for potential threats that would be identified by green blips on a radar screen. As one might imagine, radar operators could not maintain 100% vigilance for definite amounts of time—lapses which led to costly mistakes. Similar occurrences had been noted in other lengthy and monotonous target identification tasks in countries such as the United States, Great Britain and Canada (Warm & Jerison, 1984). In response to such incidents, the United Kingdom’s Royal Air Force solicited the help of Norman H. Mackworth, a British psychologist and cognitive scientist, to investigate these issues on their anti-submarine vessels (Warm & Jerison, 1984). As a way to systematically study the problem, Mackworth developed the now well-known Mackworth Clock Test (MCT) (Mackworth, 1948). Observers were required to watch a 6-inch second hand that rotated around a 10-inch diameter blank circle every second for 30 minutes to 2 hours. On occasion the second hand would jump twice the usual distance and it was this signal that subjects would have to identify as a target by pressing a Morse Key (Lichstein, Riedel, & Richman, 2000). A hit and miss was a response within and after 8 seconds respectively. Mackworth found that performance or the number of hits relative to misses decreased progressively over time (Mackworth, 1948; Mackworth, 1950). It was this finding, which is now called the vigilance decrement (see Figure 1) that set the stage for vigilance research thereafter (Warm, Parasuraman, & Matthews, 2008). Since Mackworth’s time,
several types of vigilance tasks have emerged. To this day, however, most maintain the fundamental structure Mackworth used: the identification of an infrequent signal or targets that must be parsed from frequently presented distracters or non-targets.

![Vigilance Decrement](image)

Figure 1. An example of the vigilance decrement. The above plot depicts real data from the McKinley Study (see chapter 9).

4.1 Psychophysical Variables

Since Mackworth’s classic experiments, scientists have sought to understand vigilance and why and under which circumstances the vigilance decrement occurs. Scientists have gained this insight by manipulating key psychophysical variables. Faisal, Selen, and Wolpert, (2008) classified these variables as first-order and second-order factors (summarized in table 1 below). First-order variables involve changes in the physical nature of the stimulus itself. Examples include signal intensity (i.e. brightness), duration and event rate. Second-order factors refer to variables based on the subject’s personal
interpretation of the signal or its associated characteristics derived from experience with the task, such as signal probability or type.

Table 1. This table provides a summary of common first-order and second-order factors as stated in (Faisal et al., 2008)

<table>
<thead>
<tr>
<th>Key Psychophysical Variables Affecting Vigilance Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Order Factors</strong></td>
</tr>
<tr>
<td>Sensory modality</td>
</tr>
<tr>
<td>Signal intensity</td>
</tr>
<tr>
<td>Signal duration</td>
</tr>
<tr>
<td>Background event rate</td>
</tr>
<tr>
<td>Multiple signal sources</td>
</tr>
</tbody>
</table>

4.1.1 **First-Order Factors**

Event rate (frequency of signal presentation) has long been considered one of the most influential first order factors in vigilance tasks (Parasuraman, Warm, & Dember, 1987; Warm & Jerison, 1984). Several experiments to date have shown that vigilance task performance efficiency varies inversely with background event rate—particularly, signal detection accuracy/probability and reaction time (Parasuraman, Warm, & See, 1998). See, Howe, Warm, and Dember, (1995) identified/confirmed signal salience (specific type of signal intensity) as another, if not the most important, key first-order factor in vigilance performance in a meta-analysis of perceptual sensitivity (ability to discriminate between a signal and non-signal; see “Signal Detection Theory” section). Other first-order factors include sensory modality, signal duration and the number of signal sources. Sensory modality, which describes the senses being engaged, is typically visual or auditory in vigilance tasks. Researchers may also vary the number of signal sources by using multiple sensory modalities simultaneously.
4.1.2 Second-Order Factors

The typical vigilance experiment involves the identification of relatively few signals out of several non-signals. Depending on the type of task (see “Taxonomy of Vigilance” section) changes in vigilance may represent changes in the subject’s willingness to respond. It is second-order factors that primarily influence these conscious and subconscious decisions. If a signal is less probable and/or harder to distinguish (signal spatial uncertainty) for example, a subject will be less willing to identify it as a signal. Situations like these, where subjects are making decisions in the face of uncertainty, are described by Signal Detection Theory (SDT) (see “Signal Detection Theory” section).

4.2 Task Classifications

Four task classification terms exist that are commonly used by vigilance researchers today and will be useful in discussing vigilance throughout this thesis. These vigilance tasks classifications include: simultaneous, successive, static and dynamic. Simultaneous and successive task classification terms come from the vigilance taxonomy (described below), are based off of resource theory (see “Resource Theory” section), and are often described in pairs. Similarly, static and dynamic tasks tend to be discussed together.

4.2.1 The Taxonomy of Vigilance and Successive and Simultaneous Tasks

Over the past decades vigilance researchers have struggled to generalize findings and develop theories that account for all experimental outcomes in vigilance tasks. Instead, researchers have been more successful by describing subsets of experimental data. One reason may be because of the diversity of experimental types. For example, experiments
can differ by whether the task requires memory as well as by source complexity (single vs. multiple signals), event rate (slow vs. fast) and sensory modality (auditory vs. visual).

In an effort to classify these different experimental types, (Parasuraman & Davies, 1977) developed a taxonomic system known today as the *Taxonomy of Vigilance*. As can be seen in figure 2, the taxonomy assigns source complexity, event rate and sensory modality into separate dimensions and divides tasks into two types: successive and simultaneous. *Successive-discrimination* tasks require subjects to identify targets by comparing them to a reference in memory. An example case would be when a subject must determine if a line is the same length or color as one presented in the past.

*Simultaneous-discrimination* tasks, which do not rely on memory, require subjects to identify targets in the midst of distracters or non-targets. For example, a subject might be asked to identify a “w” out of a field of “v’s” or a color out of several other presented colors.

![Figure 2. Taxonomy of Vigilance dimensions (reproduced from Parasuraman & Davies, 1977)](image-url)
Warm and Dember (1998) highlights two different tests that provide support for the vigilance taxonomy. The first test looks at correlation coefficients between and within the two task types. In this case, since the taxonomy assumes a distinction exits between successive and simultaneous tasks, one would also rationally assume that simultaneous tasks will be highly correlated to one another. Successive tasks should also be highly correlated to one another. Conversely, if successive and simultaneous tasks are truly distinct correlations between the two types should be low. Warm and Dember (1998) cite several instances of this very observation—“even across sensory modalities.” On a related note, Matthews, Davies, and Holley (1993) found stronger performance correlations between “highly demanding” tasks and successive rather than simultaneous tasks. Such an observation not only supports the simultaneous-successive task distinction but suggests that successive tasks will show greater performance declines than simultaneous.

The second test used performance feedback or “knowledge of results” (KR). The thought here was that training benefits would be more pronounced within task types (i.e. either as a successive or simultaneous task) rather than for vigilance tasks as a whole. Becker, Warm, Dember, and Howe (1994) trained subjects using KR with either a simultaneous or successive task and looked at their performance in two general cases: specific and non-specific. In the specific case subjects performed a vigilance task that was the same type as the one they trained with (i.e. within task type). Conversely, if the subject performed a task that was different than the one they trained with it was called non-specific (i.e. between task type). As expected,
the benefits of KR transfer were more pronounced in the specific condition (see Figure 3 below).

![Figure 3. From Becker, Warm, Dember, and Howe, (1994) adapted in Warm and Dember, (1998)](image)

4.2.2 Dynamic vs. Static Tasks

Vigilance researchers also make distinctions between tasks that are actively changing versus tasks that are not changing at all. In a static task a subject must identify a target simply if a signal is present. A subject might for example be asked to indicate whenever they see a red triangle. In a dynamic task the target itself may always be changing. In this case the subject would have to identify two tip-to-tip red triangles out of a constantly changing configuration of several triangles. As one might imagine, decrements are seen more in dynamic tasks (Funke, 2009).

4.3 Summary

At first glance the findings up to this point seem straightforward. Generally speaking, the harder a task is, whether the task has a higher event rate, is successive or is dynamic,
the more likely and faster an individual is going to show a vigilance decrement. What’s not so clear is the conceptualized “why” behind these intuitive results. How does one explain what exactly is happening in the brain as a result of these different types of vigilance tasks? We’ve seen that vigilance is complicated—it has multiple psychophysical variables under two orders which can be organized within three dimensions under various task types (see Figure 2). How does one relate these differences to actual performance? It is these basic questions that the theories of vigilance have attempted answer (discussed below).
5.0 THEORIES

Over the years several theories have emerged in an effort to explain vigilance and the vigilance decrement. Unfortunately, not one theory yet exists that can account for all aspects of vigilance performance. The three theories presented below, however, will be useful for interpreting vigilance performance changes. The first of the presented theories, signal detection theory (SDT), can be viewed as a statistical tool that describe changes in vigilance performance and is used in the last two presented theories, arousal and resource theory. Arousal and resource theories on the other hand, focus more on explaining why vigilance changes occur. Resource theory appears to be more popular among researchers than arousal theory (for reasons discussed below), but most likely relates to the principles of arousal theory in some form or fashion. Expectancy theory, though a theory on its own, has been coupled with SDT and is presented more as a rationale for parameter changes defined by SDT. Therefore, one should view these theories as independent units, but also as units that work together to describe vigilance performance (see Figure 4 below).

Figure 4. Popular Vigilance Theories Flow Diagram
It is important for the reader to note that the following is not meant to provide a complete description of the theories of vigilance. Rather, the below information is meant to provide a fundamental knowledge base that will enable the reader to conceptualize vigilance and make informed interpretations of the experimental results presented in this thesis.

5.1 Signal Detection Theory

Often in vigilance tasks subjects must make decisions in the face of uncertainty. Imagine a task where an observer must identify green circles that briefly appear within a static background on a television screen. At first it is very easy to identify the green circle or target. In later trials, however, the experimenter increases the task difficulty by first increasing the event rate and then adding distracters such as green squares and reducing the signal saliency. These changes result in the subject becoming less certain that what he/she is seeing is in fact a target. SDT is a statistical means to quantify and describe the decision making process involved in these situations by making distinctions between signal and noise.
Two types of noise exist in human perception—internal and external (Heeger, 1997). Internal noise refers to the inherent stochastic nature of neural activity in the brain, while external noise describes everything else—distracters, environmental events etc. (Heeger, 1997). Typically, one probability density curve, designated with the letter “n” in figure 5, describes both internal and external noise. This noise is always present whether an individual actively engages the nervous system or not (Faisal et al., 2008; Pinneo, 1966). Therefore, when a subject identifies a signal he/she is doing so in the presence of noise, whether distracter stimuli exist or not. This generalized noise is represented as a second shifted probability distribution (designated “s” in Figure 5).

Tasks, like the color/circle identification task described above, are defined as yes-no vigilance tasks. In yes-no vigilance tasks subjects must determine whether presented
information is or is not a signal, with no in-between response (i.e. no “maybe I saw” responses). Four possible results can occur (Green & Swets, 1966; McNicol, 2005):

1) Hit—subject correctly claims a signal was present. Therefore the hit rate is defined as $P(S|s)$, where “S” indicates that the subject saw a signal and “s” that an actual signal was presented.

2) Miss—subject thinks/says no signal is present when one in fact exists; $P(N|s)$, where “N” indicates that the subject did not see a signal and “s” that an actual signal was presented.

3) False alarm—subject thinks a signal is present when it was actually noise; $P(S|n)$.

4) Correct Rejection—no signal was present and the subject correctly makes no claim; $P(N|n)$.

By recording the number of hits, misses, false alarms and correct rejections during a vigilance task their respective conditional probabilities can be calculated by dividing each value by the total number of test events. These probabilities can then be used to calculate test subject perceptual sensitivity, $d'$ and their observing criterion, $\beta$.

5.1.1 **Perceptual Sensitivity**

Perceptual sensitivity (also called “discriminability” and the “sensitivity index”), as mentioned earlier, describes how well the test subject can distinguish between a signal and noise. Statistically speaking, this can be described as the normalized distance between the two mean values of the noise and signal plus probability density curves (see equation 3).
\[ d' = \frac{\bar{X}_s - \bar{X}_n}{\sigma_n}, \] where \( \bar{X}_s \) is the mean signal distribution value, \( \bar{X}_n \) is the mean noise distribution value and \( \sigma_n \) is the standard deviation of the noise distribution (McNicol, 2005) (Equation 3)

Therefore, the larger \( d' \) is, the farther apart the probability distribution curves and the easier it is to identify signals.

5.1.2 Observer Criterion

The observer’s criterion is the point on the subject’s sensory continuum that divides the “yes” and “no” region. It describes how “strict” or “lax” a subject is being in determining whether presented information is a signal or noise, and its sensory continuum position is the motivation for conditional probability values. A more conservative or higher \( \beta \) will lead to less false alarms at the cost of a decreased hit rate while less stringent or lower \( \beta \)'s will lead to more hits in addition to more false alarms. \( \beta \) can be calculated by dividing the height of the signal distribution, \( y_s \), by the height of the noise distribution, \( y_n \), described in equations 4, 5 and 6 below (McNicol, 2005).

\[ y_n = e^{-\frac{1}{2}x^2} \] (Equation 4)
\[ y_s = e^{-\frac{1}{2}(x-d')^2} \] (Equation 5)
\[ \beta = \frac{y_s}{y_n} \] (Equation 6)

where “x” is the distance from x-axis position of the criterion to \( \bar{X}_n \). This value is equivalent to \( z(S|n) \), which is the z-score relating to \( P(S|n) \) (can be found using a statistical table).

It is important for the reader to note that \( \beta \) is not the actual x-axis position but rather provides a quantitative sense of bias towards either the noise or signal distribution. In
other words, a $\beta$ equal to one will describe no bias while a $\beta$ less than or greater than one describe biases towards noise and signal distributions respectively. Researchers often employ additional strategies to characterize $\beta$ (such as log-log plots) but these methodologies are beyond the scope of this thesis.

Typically, individuals will have less conservative or lower decision criterion values and then increase the value until it converges onto an optimal one (Matthews, Davies, Westerman, & Stammers, 2000; Warm & Jerison, 1984). It is also possible, however for the reverse to be seen with a corresponding vigilance increment (improved vigilance performance). These general findings can best be explained by expectancy theory (Matthews, Davies, Westerman, & Stammers, 2000).

5.1.3 *Expectancy Theory*

In the application of expectancy theory it is thought that criterion shifts are a result of a subject’s changing perception or “expectation” of signal probabilities. Initially, subjects might believe signal probabilities are higher than they actually are. As they gain experience in the task, however, they correct for this underestimation by raising the value of $\beta$. In less often cases, subjects might have overestimated $\beta$ values and similarly adjust/equilibrate their criterion by lowering it as they get more experience with tasks. This view of criterion shifts can be supported by the observation that subjects tend to perform better when provided knowledge of their results (KR) (i.e. performance feedback) and how using different signal probabilities have sometimes influenced $\beta$ values (Szalma, Hancock, Dember, & Warm, 2006; Hitchcock, Dember, Warm, Moroney, & See, 1999; Baker, Ware, & Sipowicz, 1962). It is thought that when a subject has a sense of how he/she is performing they are in a better position to make criterion
adjustments and do so faster, while training probabilities influence an individual’s “expectation” of signal probabilities during actual experimentation (Matthews et al., 2000).

5.1.4 Closing Remarks

Since the proposed application of SDT to vigilance studies vigilance researchers have successfully used SDT as a tool to measure perceptual sensitivity and decision criterion to date (Warm & Jerison, 1984; Matthews et al., 2000). As stated by Mathews et al., 2000, many vigilance studies using SDT have shown that the vigilance decrement is due to progressively increasing decision criterion values. Vigilance decrement, however, in a smaller subset of experiments can be attributed to changes in perceptual sensitivity (See, Howe, Warm, & Dember, 1995). It is important to note, however, that SDT measures ($\beta, d^\prime$) do not describe all cases where vigilance decrements occur.

5.2 Arousal Theory

The arousal theory of vigilance (or activation theory) generally states that vigilance decreases as an individual’s arousal decreases (Parasuraman, 1985). Although various definitions of arousal exist (see Oken, Salinsky, & Elsas, 2006), such as a “readiness to respond” (Matthews & Davies, 1998), most vigilance researchers think of arousal as a state of alertness that varies along some continuum from an intense sleep state to an extreme wakeful state (Humphreys & Revelle, 1984; Matthews & Davies, 1998; Oken et al., 2006; Parasuraman, 1984). Early work by Hebb (1958) suggested that sensory input not only contained information to be processed but also served as an input required to maintain alertness. The impact of this input depended on stimulus variation. Therefore, as Buck’s (1966) (as cited in Parasuraman, 1985, p. 500) refined arousal theory proposes,
if sensory input variation is not above an arbitrary set point the subject becomes “underaroused” and consequently exhibits a vigilance decrement.

Much experimental evidence supports the idea that arousal plays a role in vigilance. As one might expect, vigilance performance shows improvement when subjects take stimulant drugs (Koelega, 1993; Prokopova, 2010) (e.g. caffeine, nicotine, epinephrine and amphetamines), and a decline when they take inhibitory drugs (e.g. alcohol, hyoscine and chlorpromazine) (see Hitchcock, 2000). Environmental stressors, which influence arousal, also affect vigilance performance. Researchers, for example, have shown that exercise and music improve vigilance performance (Wolfe & Noguchi, 2009), while heat and noise have been shown to decrease vigilance performance (Vallet, 2001).

In some cases electrocortical measures of arousal, such as electroencephalography (EEG), skin conductance and event related potential (ERP) measures, have also correlated with vigilance performance. Both EEG alpha activity and skin conductance decrease in sleep and are therefore measures of lowered arousal (Carlson, 2010; Lee, Kim, & Suh, 2003). Researchers over the years have successfully related these indices to vigilance performance have shown that these same indices somewhat follow vigilance decrements (Parasuraman, 1984; Yu, Lu, Ouyang, Liu, & Lu, 2010). Furthermore, electrodermal labiles (individuals with high frequency of spontaneous skin conductance; typically introverts) have shown superior performance in vigilance tasks in several instances compared to electrodermal stabiles (individuals with a low frequency of spontaneous skin conductance; typically extroverts)— although these results have been mixed (Hastrup, 1979; Sakai, Baker, & Dawson, 1992; Koelega, 1992).
It is difficult, however, to apply arousal theory to vigilance performance generally. This is for two reasons. The first is because many ways exist to measure “arousal” and they do not all correlate with one another. The fact they all don’t correlate well to each other suggests that each measure is describing something slightly different. The second is because these arousal measures don’t always correlate with vigilance performance decrements themselves (Ballard, 1996).

Arousal measures can be split into autonomic arousal or electrocortical arousal categories (Parasuraman, 1984). Autonomic arousal measures are those such as heart rate indices, blood pressure, skin conductance and measures of blood/urine drug levels (e.g. adrenalin) (Oken et al., 2006; Parasuraman, 1984). According to Parasuraman (1984), autonomic measure-vigilance relationships are highly variable and thus not robust. Biochemical measures or drug measures, as mentioned above, provide the best evidence. Electrocortical measures, however, which are primarily those found using EEG, have shown more consistent results.

Parasuraman (1984) maintains, however, that arousal theory cannot “warrant any strong conclusions regarding the mechanisms of the decrement.” Such variable results might be accounted for by the inverted U hypothesis (or Yerkes-Dodson law) concept of arousal theory. The hypothesis suggests that optimum performance occurs in some medium between opposite poles of the arousal spectrum. By this hypothesis therefore, subjects can actually be too aroused in addition to being under-aroused—leading to corresponding performance decrements. While the concept might explain overall experimental variability, however, it makes it difficult to specifically describe the vigilance decrement itself.
More recent research, performed by Warm, Matthews, and Parasuraman (2009), appears to discount arousal theory’s role in vigilance all together. They found that regional cerebral blood flow (rCBF), which has been historically correlated with the vigilance decrement, did not decline when subjects were not given a “work imperative.” In other words, subjects stared at a screen while a vigilance test ran—an arguable very un-arousing task that should, by arousal theory, lead to a vigilance decrement. Yet no decrement was seen.

In light of the conflicting results supporting and discounting arousal theory many vigilance researchers think of arousal as affecting the level of vigilance overall but not so much the decrement specifically (Parasuraman et al., 1998; Parasuraman, 1985). Rather, it is often said that arousal may play a role in the vigilance decrement at times but is not necessary for decrement. The variability also suggests that vigilance in itself is not a unitary process and cannot be described by one mechanism (see “Taxonomy of Vigilance” section).

5.3 Resource Theory

Imagine a toy car that runs on batteries. When the batteries are fresh, the car runs at 100%. As time progresses and the batteries become weaker, however, the car’s performance begins to decline. Resource theory is much like this scenario except the brain is the car and “attentional processing resources” are the energy/fuel provided by the car’s batteries. Specifically, resource theory assumes that cognitive processing relies on a limited pool of resources that, when used up, lead to performance decrements (as cited in Hancock and Szalma, 2000, p. 3: Kahneman, 1973; Norman & Bobrow, 1975; Navon and Gopher 1979; Wickens, 1980; Wickens, 1984).
5.3.1 **Resource and Data Limited Processing**

A useful way to look at resource theory is by examining the following formula:

\[ P \propto \frac{R}{D}, \text{ for resource limited processing} \]

\[ P \neq \frac{R}{D}, \text{ for data limited processing}, \]

where \( P \) is performance, \( R \) describes the amount of allocated resources and \( D \) describes the task demand (see Matthews et al., 2000).

*Resource limited processing* describes cases where performance is dependent on resource allocation. In these situations therefore, declines in attentional resources and/or increases in task demand will lead to performance decrements. Or if one were trying to maintain performance levels (\( P \)) during an increase in task demand (\( D \)) he/she would have to restore/maintain the resource-to-task demand ratio (\( R/D \)) by increasing resource allocation (\( R \)). During *data limited processing* on the other hand, such as in a task that isn’t cognitively challenging or is extremely challenging, resource allocation doesn’t make a difference in performance (see Matthews et al., 2000). These constraints are consistent with findings that have shown little to no vigilance decrement under conditions of low cognitive demand (e.g. Hitchcock et al., 2003) and follow Korol and Gold’s (1998) notion (as cited in Warm et al., 2009) that an individual must be sufficiently challenged before he/she shows measurable performance and/or resource decline (e.g. blood flow velocity).
5.3.2  *Unitary and Multiple Resource Theories*

In general, vigilance researchers take either a unitary or multiple resource approach to describing the vigilance decrement. Unitary approaches assume that only one “pool” of resources exist from which to draw from while multiple resource approaches assume different types of processing mechanisms draw from separate pools (i.e. multiple resource pools exist) (Matthews et al., 2000). For example, the most general unitary resource theory, proposed by Parasuraman, et al. (1987), explains differences between successive and simultaneous tasks by assuming that successive tasks are more resource demanding and that individual differences are more pronounced in these.

5.3.3  *SIT and STM Resources*

Conversely, Humphreys and Revell’s (1984) multiple-resource theory, classifies resources into two types: sustained information transfer (SIT) and short-term memory (STM) resources. Humphrey and Revell (1984) go further to suggest that arousal enhances and suppresses SIT (associated with simultaneous tasks) and STM resource availability (associated with successive tasks) respectively. Since simultaneous tasks depend on SIT resources and successive on STM multiple resources, resource theory predicts that arousal enhances simultaneous discrimination tasks but hinders successive (Matthews & Davies, 1998). Such a prediction makes logical sense. A relatively easier task that does not rely on memory, might benefit from increased arousal, while a

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1 *SIT*—tasks which “the subject is required to process a stimulus, associate an arbitrary response (Posner, Snyder, & Davidson, 1980) to the stimulus, and execute the response. Furthermore, there is no appreciable retention of information required nor is there an appreciable amount of distraction”, Humphreys & Revelle, 1984, p. 161.

*STM*—tasks that “require subjects to either maintain information in an available state through rehearsal or other processes or retrieve information that has not been attended to for a short time”, Humphreys & Revelle, 1984, p. 164.
relatively more difficult task might be hindered by increased arousal. In fact, similar findings in social facilitation across species who under observation—an arguably arousing scenario, show improved and decreased performance on tasks they are skilled at and not skilled at respectively (see Aiello & Douthitt, 2001).

5.3.4 Closing Remarks

Regardless of the approach, Warm et al. (2008) and Matthews et al. (2000) describe several experiments that provide “converging evidence” for resource theory. Warm et al. (2008) lends support to the unitary resource theory by discussing several instances where successive tasks showed more performance deficits than simultaneous tasks under conditions of known high level information processing demand. In addition to high within-category and low cross-category correlation coefficients (successive vs. simultaneous), Warm et al. highlight how signal saliency, spatial uncertainty and event rate have all shown correspondence with well established workload measures (e.g. NASA-Task Load Index). Imaging studies that provide direct measures of resources show support for resource theory as well. Regional cerebral blood flow (rCBF) or cerebral blood flow velocity (CBFV) and regional oxygen saturation (rSO₂) values have often paralleled the vigilance decrement (see “Blood Flow and Cerebral Oxygenation” section for more detail). Matthews et al. (2000) also discusses how vigilance may have relations with controlled processing, which has been shown to be highly resource demanding.

It is not clear, however, whether unitary or multiple resource theories are most appropriate and how resource depletion actually works (Matthews et al., 2000). As discussed, workload seems to play a major role in vigilance performance, but it has not
been identified whether these high workload conditions increase the rate of resource depletion or if changes are due more so because of motivational factors (Matthews et al., 2000). If a subject becomes less motivated throughout a task because of high workload, for example, performance decrements may result because subjects have reduced their resource allocation—whether conscious or subconscious.

5.4 Where Vigilance Theories Are Now

In terms of theorizing vigilance where is it now? Today most vigilance researchers lean more towards resource theory (though this is not the case for all) while using SDT as a tool to derive the source of changes in vigilance performance. This tendency is largely influenced by the ability of relatively new imaging technologies to monitor “resources” continuously and the observed parallel with vigilance performance (see “Blood Flow and Cerebral Oxygen Saturation Techniques” section below). The role of arousal, however, is not entirely ignored, and it is generally agreed that arousal at least impacts overall vigilance performance (i.e. vigilance level). Some researchers even argue that arousal is the fuel or resource-allocation determinant in resource theory (see Warm, Matthews, & Finomore, 2008). A general sense exists, in addition, that vigilance is multi-dimensional (is not unitary), and to the author’s knowledge, no theory to date can account for all vigilance outcomes. Parasuraman et al. (1987) vigilance taxonomy, however, has successfully provided a framework to first categorize and then make generalizations about vigilance performance outcomes (see “The Taxonomy of Vigilance” Section ).

Generally, in terms of the behavior of vigilance performance, the harder the task the more the decrement. Particularly, event rate and perceptual sensitivity seem to be the two most important psychophysical variables in vigilance tasks, while successive and
dynamic tasks show the most decrement. Matthews et al., (2000) conclude that decision criterion changes, which can best be explained by expectancy theory, happen more so in low event rate tasks. Conversely, sensitivity decrements are more present in high event rate successive tasks while poor perceptual sensitivity causes greater decrements in simultaneous tasks.
This chapter will describe the brain regions associated with these systems in two separate sections, the arousal/sleep wake systems section and the general vigilance systems section (Figure 6). Each section will conclude with a conceptualized flow diagram that depicts how each system ties into the themes presented thus far in this thesis. These arousal and vigilance flow diagrams are then combined at the end of the chapter to form a Concluding Conceptual Framework that will serve as the basis for interpreting vigilance decrement results in this thesis.
6.1 Arousal/Sleep Wake Systems

6.1.1 Wakefulness-promoting Brain Regions and Neurotransmitters

The arousal/sleep-wake system (Figure 7) centers around the interaction of a region dedicated to promoting wakefulness and regions dedicated to promoting sleep. The wakefulness promoting regions of the brain include the basal forebrain (BF), pedunculopontine (PPT), laterodorsal tegmental nuclei (LDT), locus coeruleus (LC), raphe nuclei and tuberomammillary nucleus (Saper, Scammell, & Lu, 2005 and as cited in Carlson, 2010: Sherin et al., 1998; Gvilia et al., 2006; Suntsova et al., 2007). Each of these brain regions are known for secreting specific neurotransmitters which are summarized in Table 2.
Table 2. Sleep-promoting vs. Wakefulness-promoting Regions

<table>
<thead>
<tr>
<th>Regions</th>
<th>Brain Structures</th>
<th>Neurotransmitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-promoting</td>
<td>Ventrolateral preoptic area (vlPOA)</td>
<td>Gamma-Aminobutyric acid (GABA)</td>
</tr>
<tr>
<td>Wakefulness-promoting</td>
<td>Pendunculopontine (PPT)</td>
<td>Acetylcholine (ACh)</td>
</tr>
<tr>
<td></td>
<td>Laterodorsal tegmental nuclei (LDT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal Forebrain (BF)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Locus Coreulus (LC)</td>
<td>Norepinephrine (NE/NA)</td>
</tr>
<tr>
<td></td>
<td>Raphe Nuclei (RN)</td>
<td>Serotonin (5-HT)</td>
</tr>
<tr>
<td></td>
<td>Tubermammillary nucleus (TMN)</td>
<td>Histamine (His)</td>
</tr>
<tr>
<td></td>
<td>Lateral Hypothalamus (LH)</td>
<td>Orexin (ORX)</td>
</tr>
</tbody>
</table>

The neurons that secrete these neurotransmitters then form connections with upper brain regions that are necessary for promoting “cortical activation and behavioral arousal” (Figure 8; see Carlson, 2010).

Figure 8. Wakefulness-promoting brain region neurotransmitter systems (from Saper, Scammell, & Lu, 2005)
6.1.2 Sleep-promoting Brain Regions and Neurotransmitters

Most of the body’s sleep-promoting neurons are located in the ventrolateral preoptic area (vlPOA) located in the hypothalamus (Lu et al., 2000 as cited in Carlson, 2010). As depicted in figure 9, the vlPOA forms inhibitory synapses (GABAergic) with the wakefulness promoting regions of the brain. Therefore, the greater the activity in the vlPOA, the less the activity in the wakefulness promoting regions (i.e. the vlPOA promotes sleep). It turns out, however, that the wakefulness-promoting neurons also form inhibitory synapses with the vlPOA, which when more active lead to wakefulness. This type of interaction is referred to as “mutual inhibition” and forms the basis of the sleep-wake flip-flop described in the section below.

Figure 9. Wakefulness-promoting brain regions inhibited by the ventroloateral preoptic area (from Saper, Scammell, & Lu, 2005)
6.1.3 The Arousal/Sleep-Wake Flip-Flop

As mentioned previously, the sleep-promoting and arousal-promoting regions mutually inhibit one another (Chou et al., 2002 as cited in Carlson, 2010). That is, sleep-promoting neurons of the vlPOA form inhibitory synapses with regions of wakefulness promoting regions, and wakefulness promoting regions form inhibitory synapses with the sleep-promoting neurons of the vlPOA. The more active a region the more it will inhibit the other, and since these two regions inhibit one another only one can be completely active at a time (Saper et al. 2001 as cited in Carlson, 2010). If the sleep-promoting region is more active, for example, it will inhibit the wakefulness-promoting region, which decreases its activity and effectively decreases the amount of inhibition it exerts on the sleep-promoting region. Figure 10 provides a depiction of this example (bolder lines signify greater activity or dominance). This property of either being in an “on” state or “off” state is known as a flip-flop (analogous to an electronic circuit flip-flop).

![Figure 10. A depiction of the sleep/waking flip-flop (adapted from Carlson, 2010). In this case the sleep-promoting region is more active than the wakefulness-promoting region.](image-url)
So what drives the flip-flop—that is what pushes our sleep-promoting region or wakefulness-promoting regions to be active? The two main inputs/drivers for the sleep-promoting and wakefulness-promoting regions are the quantity of the molecule adenosine and the orexigenic neurons respectively. Adenosine works by decreasing neural activity in regions that promotes wakefulness and by increasing neural activity in regions that promote sleepiness. Conversely, orexin works by increasing neural activity in areas that promote wakefulness and vice versa for those that promote sleepiness (for additional details see below).

6.1.4 **Adenosine As A Sleep-promoting Region Driver**

![Figure 11. A sleep/wake flip-flop depiction incorporating adenosine as a sleep-promoting driver (adapted from Carlson, 2010)](image)

Adenosine levels increase over periods of prolonged waking and decrease during periods of sleep (Porkka-Heiskanen, Strecker, & McCarley, 2000 as cited in Carlson 2010). This increase of adenosine leads to drowsiness (Carlson 2010, Porkka-Heiskanen 2010).
et al. 2002). Porkka-Heiskanen et al. (2002) hypothesize (for which they provide evidence) that adenosine, an inhibitory neuromodulator, serves to decrease neural activity as an energy-balance protective mechanism. Indeed, adenosine level increases follow glycogen (energy-storage) level declines that are caused by the metabolic need/usage of neural activity throughout the day (Carlson 2010). Porkka-Heiskanen et al. (2002) also suggests that energy depletion signals the increase in extracellular adenosine that inhibits activity in the basal forebrain and other related structures (see their article for supporting evidence). Additionally, Scammell et al., (2001) in Carlson (2010) show how adenosine actually increases activity in the vlPOA (in mice) in addition to decreasing activity in wakefulness-promoting regions such as histaminergic neurons. Put simply, converging evidence suggests that the accumulation of adenosine throughout the day promotes the flip-flop from the wakefulness-promoting region to sleep-promoting region (see Figure 11).
6.1.5 Orexinergic Neurons As A Wakefulness-promoting Regions Driver

Figure 12. A sleep/wake flip-flop depiction incorporating orexin as a wakefulness-promoting driver (adapted from Carlson, 2010)

Orexins (or hypocretins) are a pair of excitatory neuropeptide hormones whose neuronal cell bodies are mostly found in the lateral hypothalamus (see Table 2 and Figure 9). These neurons form connections to most parts of the brain, including the wakefulness promoting regions mentioned earlier. When the brain receives input that requires arousal, such as hunger, satiety, biological clock/time of day and the motivation to stay awake
signals, orexinergic neurons show increased activity. Since orexinergic neurons form connections with the listed wakefulness promoting regions and they are excitatory, increased orexinergic activity pushes the sleep/waking flip-flop to the arousal state (see Figure 12; Carlson 2010).

6.1.6 **Putting it all together**

It turns out that in addition to directly inhibiting wakefulness promoting regions the sleep promoting region also inhibits the orexinergic neurons. Therefore, increased adenosine levels, which stimulate the sleep-promoting region, also indirectly decrease wakefulness-promoting activity by inhibiting orexinergic activity (see Figure 13). Conversely, sufficient increased orexinergic input signals (e.g. hunger) indirectly lead to decreased
inhibition of the orexinergic neurons, which ultimately contributes to sleep/waking flip-flop switch to the arousal state (Carlson, 2010).

6.1.7 The arousal-vigilance pathway

Figure 14. Flow-chart of the arousal-vigilance pathway

The arousal/sleep wake systems can be organized into an arousal-vigilance pathway (which will be useful later; Figure 14). Remember that the arousal/sleep wake system has various molecules that form part of or feed into the arousal/sleep wake systems (e.g. Adenosine, Orexin, NE)—this is represented by the system inputs box. Other hormones (e.g. cortisol) and endocrine systems, as well as general molecules carried by the bloodstream—represented as “hemodynamic” (e.g. glucose and oxygen) also feed into the arousal/sleep wake system because they have been shown to influence arousal (Nishino & Sakurai, 2006). These system inputs usually change in response to something external to themselves, which is represented by the system input drivers. Key system drivers include cognitive task demands (e.g. first and second order factors, successive vs. simultaneous and static vs. dynamic tasks), motivational (e.g. risk and monetary related) and environmental factors (e.g. temperature and background noise). Therefore, an
individual who engages in a both cognitively challenging and motivationally important task (system input drivers) might release stress hormones, have increased blood flow and increased noradrenergic activity (system inputs) which results in increased arousal and resultantly better overall vigilance performance. The system drivers can also directly influence arousal/sleep wake systems. For example, a warm environment can shift the sleep/wake flip-flop to the sleep-promoting region in the arousal/sleep wake system.

6.2 General Vigilance Systems

![Diagram of vigilance systems](image)

Figure 15. “General vigilance systems” influence vigilance performance

As mentioned previously, brain regions involved in vigilance performance can be organized into those dedicated to arousal and those dedicated to vigilance performance. This section serves to identify and discuss the brain regions dedicated to vigilance performance (Figure 15). As the reader will see, arousal and vigilance systems cannot be
completely separated into categories but rather interact together to influence vigilance
performance.

6.2.1 Bottom-up vs. Top-Down

The discussed brain regions are organized into three different groups: bottom-up
processors, top-down processors, and neurotransmitter systems. Bottom-up processes are
“sensory-driven and automatic”—they are in response to something external (Bushman,
2008). An example case would be a loud noise or bright flash of light on a screen that
immediately draws an individual’s attention. Top-down processes, in contrast, are
“knowledge-driven” (Fassbender, et al., in press)—which is internal (Bushman, 2008).
Factors like motivation, development of expectations, knowledge of target location and
so forth enact top-down processes (Sarter, Givens, & Bruno, 2001). These top-down
processes then interrupt bottom-up processes in cases where bottom-up processing is not
important (Norman & Shallice, 1986 in Fassbender et al., in press). For example, an
investigator might tell a study participant that sporadic noises and flashes of light will
occur but that he/she should ignore these and focus on the specified task. In this case,
bottom-processing enacted by the loud noise and/or bright flash would be interrupted by
top-down processing, because the subject recognizes that these stimuli should be ignored.
Bottom-up and top-down processors, therefore, refer to brain structures involved in these
bottom-up or top-down processes respectively. Neurotransmitter systems, on the other
hand, refer to brain structures and the neurotransmitters they secrete. Often, these
systems serve as mediators between bottom-up and top-down processors.
6.2.2 Discussed Brain Regions

The brain regions that this section will discuss are summarized in table 3. Bottom-up and top-down processors include regions in the parietal cortex and thalamus and the dorsolateral prefrontal cortex and the cingulated gyrus (cortex) respectively. The parietal cortex, as depicted in figure 16.1, is the lobe located immediately caudal (behind) to the central sulcus, while the thalamus sits on top of the brainstem. The dorsolateral prefrontal cortex is situated near the front and to sides of the frontal cortex, which is the lobe rostral (in front of) to the central sulcus (see Figure 16.1 and Figure 16.2).

Table 3. Summary of “General Vigilance System” Bain Regions

<table>
<thead>
<tr>
<th>Brain Region Type</th>
<th>Brain Region (\rightarrow) Neurotransmitter (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottom-up Processors</td>
<td>Parietal Cortex, Thalamus</td>
</tr>
<tr>
<td>Top-down Processors</td>
<td>Dorsolateral Prefrontal Cortex (dIPFC), Cingulated Gyrus (Cortex)</td>
</tr>
<tr>
<td>Neurotransmitter Pathways</td>
<td>Locus Coeruleus (LC) (\rightarrow) Norepinephrine (NE)</td>
</tr>
<tr>
<td></td>
<td>Raphe Nuclei (RN) (\rightarrow) Serotonin (5-HT)</td>
</tr>
<tr>
<td></td>
<td>Basal Forebrain (\rightarrow) Acetylcholine (Ach)</td>
</tr>
</tbody>
</table>

Of the three discussed neurotransmitter systems, two reside in the brainstem while the final is located in the basal forebrain. The two structures located in the brainstem (the trunk-like set of brain structures located below the cerebral cortex) are the locus coeruleus (LC), which is known for secreting norepinephrine (NE) and the raphe nuclei (RN), which is known for secreting serotonin (5-HT). The discussed basal forebrain neurotransmitter is acetylcholine (Ach). These structures are depicted in figure 16.3.
Figure 16. Depictions of the General Vigilance Systems Brain Regions. Figure 16.2 is adapted from Carol Donner. Figure 16.3 is adapted from Saper, Scammell and Lu, 2005²

² Figure 16.1 was taken from soe.ucdavis.edu/.../eghbalis/Notes/U12Notes.html and Figure 16.2 from www.thjuland.net/limbic2.htm
6.2.3 Top-down Processors

6.2.3.1 Dorsolateral Prefrontal Cortex

Several imaging studies have shown that the dorsolateral prefrontal cortex (dlPFC) (Figure 17) is involved in vigilance performance, particularly in the right hemisphere. Studies in Breckel, Giessing, and Thiel (2011) saw decreased neural activity in the right dlPFC that paralleled the vigilance decrement over time. In Sarter, Givens, and Bruno (2001) “consistent” dlPFC activation is more specifically attributed to the right medial and frontal portions of the dlPFC in another subset of imaging studies. As discussed in Shimamura (2000), converging evidence suggests that the prefrontal cortex “mediates executive control” by acting as a “selective gating or filtering mechanism that controls information processing.” If this is the case, the right dlPFC may direct other brain regions in the processes necessary to filter out distracters (i.e. noise) while trying to

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3 Figure 17 was taken from http://www.shockmd.com/2009/01/16/neurobiology-of-psychosocial-stress-and-depression/
identify targets in a vigilance task. Studies have also shown that the prefrontal cortex plays a role in various forms of memory (including working memory) (Braver et al., 1997; Buckner & Peterson, 1996)—a cognitive skill set necessary for successive vigilance tasks.

6.2.3.2 Cingulated Cortex (Gyrus)

Figure 18. Depiction of the anterior and posterior cingulated gyri (cortices) (adapted from Pessoa, 2008)

Another area, commonly cited as showing activation changes during vigilance tasks is the cingulated cortex (Lim et al., 2010; Breckel, Giessing & Thiel, 2011; Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003). This is most particularly in the anterior (ACC) and posterior cingulated cortices (PCC) (Figure 18). The ACC is suited to function as a top-down processor because it is connected with the prefrontal and parietal cortices in addition to the motor system and the frontal eye fields (Posner and
DiGirolamo, 1998). As Bush, Luu and Posner (2000) review, the ACC is thought to function as the “brain’s error detection and correction device”—serving as a relay station that integrates and processes sensory, motor, cognitive and emotional information. If this is the case, the ACC may play the role of identifying vigilance task noise (which indirectly contributes to identifying targets) and communicating this information to other brain structures (e.g. dIPFC, motor cortex, and parietal cortex). The PCC also forms connections with the dIPFC (Pandya, Van Hoesen & Mesulam, 1981) and may play in vigilance by influencing spatial attention (Small et al., 2003).

6.2.4 **Bottom-up Processors**

6.2.4.1 **Parietal Cortex**

As in the dIPFC, studies by Breckel et al. (2011) showed decreased neural activity in the right inferior parietal cortex that paralleled the vigilance decrement over time. The parietal cortex (or parietal lobe; Figure 19) is often referred to as the somatosensory

![Figure 19. Depiction of the parietal cortex](image_url)
association cortex\(^4\) (Carlson, 2010). Critchley (1953) (as cited in Behrmann et al., 2004) appropriately describes the parietal cortex as situated at the ‘crossroads of the brain’ as it forms connections with the visual, auditory and tactile cortices of the brain (Behrmann et al., 2004). By forming these connections with other brain regions, the parietal cortex plays a role in “transforming sensory input into motor output” (Behrmann et al., 2004; Buneo & Anderson, 2006). In relation to vigilance tasks, the parietal cortex may serve to translate task sensory information (i.e. the target and distracter information during a vigilance task) into the motor command corresponding to a particular event (e.g. a mouse-click during target presentation). As a sensory driven bottom-up processor (Sarter et al., 2001), the parietal cortex may provide information to the dlPFC for additional processing during visual events (i.e. externally driven) discussed in Buschman, 2008.

6.2.4.2 Thalamus

4 The parietal cortex can also be divided into the somatosensory cortex and the posterior parietal cortex (see Behrmann, Geng, & Shomstein, 2004)

5 Figure 20 (left) was adapted from http://apbrwww5.apsu.edu/thompsonj/Anatomy%20%20Physiology/2010/2010%20Exam%20Reviews/Exam%20Review/thalamus-hypothalamus.jpg
As is the case in many of the above brain regions, thalamic activity has been shown to decrease with vigilance performance (Breckel et al., 2011; Coull, 1998). Interestingly, Portas et al. (1998) provide evidence suggesting that the thalamus (Figure 20) plays a role in mediating the interaction of attention and arousal in humans. The group had subjects perform an attentional task, either in a state of low arousal (induced by sleep deprivation) or high arousal (induced by administering caffeine) while undergoing fMRI. The highest activation levels were seen in the low arousal condition compared to the highest arousal condition (which was attributed to the thalamus having to ‘work harder’). The authors were careful to note that these effects were not seen in sleep deprivation and low arousal conditions alone but only when attention was required. The authors also saw activation in other brain regions but only the thalamus changed as a function of arousal.

The idea of the thalamus serving as the link between arousal and attention (in this case vigilance) follows suit with what has been discussed so far. Earlier the noradrenergic (NA) system of the locus coreulus (located in the dorsal pons of the brainstem) was described as being a part of the sleep/arousal wake system (see “Sleep/Arousal Wake System” Section). This is because noradrenergic activity has been shown to decline as animals move from waking states to deeper and deeper stages of sleep (i.e. decreased arousal) (see Carlson, 2010). It turns out these noradrenergic neurons have projections

Figure 20 (right) was adapted from http://fultoncountybraininjursupportgroup.health.officelive.com/images/brainstem-large.jpg

47
that also terminate in the thalamus (i.e. neurons that secrete norepinephrine form connections that end in the thalamus) (Sarter et al., 2001). The thalamus then forms connections with the cerebral cortex (i.e. either directly or indirectly with vigilance brain regions like the dlPFC, cingulated and parietal cortices as well as sensory areas (Steriade, 2001). A decline in arousal, therefore leads to decreased noradrenergic activity, which is processed and responded to by the thalamus and sent to cerebral cortex, resulting in changed vigilance performance (e.g. vigilance decrement).

The thalamus might also be responsible for (and hence explain) the inconsistent relationships found between arousal and vigilance performance (see Arousal Section). As Portas et al., (1998) suggested, the thalamus in these situations may compensate for decreased arousal by increasing neural activity. Arousal metrics, in this case, would indicate decreased arousal but relatively stable vigilance performance. With time, however—as would fall suit with resource theory, this increased thalamic neural activity would decline and correspondingly lead to declines in the vigilance brain regions of the cerebral cortex (explaining the observation that arousal affects vigilance overall but not the vigilance decrement per se).

---

6 Recall that declines in arousal did not always parallel the vigilance decrement but that decreased arousal seemed to have an overall effect on vigilance level.
6.2.5 Neurotransmitter Systems and Structures

6.2.5.1 Brainstem Structures

Generally speaking, Parasurman, Warm, and See, (1998) attribute the brain stem’s importance to vigilance by highlighting studies showing decreased vigilance performance in individuals who have had brain stem damage. More specifically, as mentioned earlier the LC, which is located in the dorsal pons of the brainstem (Figure 16.2, Figure 16.3), has long been thought to play a role in vigilance (Carlson, 2010) and may do so by interacting with the thalamus (which links arousal to vigilance effects; see “Thalamus” section). Another brainstem structure that may attribute to vigilance, is the raphe nucleus (RN) (Figure 16.2, Figure 16.3). The RN mainly functions to secrete serotonin (5-HT) (Briley & Moret, 1993). In addition to having arousal effects (see “Sleep/Wake Systems” section), 5-HT has also been shown to influence vigilance performance. Wingen, Kuypers, van de Ven, Formisano, and Ramaekers, (2008) showed that increased 5-HT lead to decreased neural activity in areas commonly associated with vigilance (e.g.
thalamus and prefrontal areas). The authors suggested that 5-HT inhibited dopamine release in the thalamus and caudate nucleus. Since these brain structures form connections with other brain areas associated with vigilance this decreased dopaminergic activity would then lead to decreased vigilance.

6.2.5.2 Basal Forebrain

As discussed in Sarter et al. (2001), another potential mediator is the basal forebrain, which has cholinergic neurons that form connections with vigilance brain regions in the cortex. Sarter et al., (2001) hypothesize that the BF is activated by the prefrontal cortex and that these cholinergic projections, which are connected to “all cortical regions and layers, facilitate all aspects of the top-down regulation of sustained attention performance.”

6.2.6 The General Vigilance Systems Pathway

![Flow-chart of the general vigilance systems pathway](image)

Figure 22. Flow-chart of the general vigilance systems pathway
Much like in the Arousal/Sleep Wake Systems section, the discussed brain regions, represented as “vigilance systems”, can be conceptualized into a “General Vigilance Systems” pathway (Figure 22). “Cognitive Task Demands,” a System Input Driver, can influence General Vigilance Systems either directly or indirectly by driving changes in System Inputs like blood glucose levels (a “hemodynamic molecule”). Neural activity then changes in the General Vigilance Systems which results in changes in Vigilance Performance. For example, a subject that is instructed to look for a particular target (a cognitive task demand) might have increased dIPFC (which is a part of the General Vigilance System) activity because it is a top-down processor (remember filtering information is a top-down process) to enact vigilance performance. This increased activity would cause blood flow changes (system inputs) to account for/in response of increased oxygen consumption during cell metabolism. After a period of time, however, these resources decline (manifested as decreased amount of system inputs), leading to decreased dIPFC activity and corresponding vigilance performance (i.e. a vigilance decrement).

6.3 Concluding Conceptual Framework

We have seen that the brain regions of vigilance performance can be conceptualized into both an arousal/sleep wake and general vigilance systems pathway. In actuality, these two systems interact together to influence vigilance performance. Recall, for example, that the impact of the thalamus, which is thought to serve as a link between arousal and vigilance, is influenced by noradrenergic and serotonergic projections originating from the brainstem (see Thalamus section). On the other hand, arousal/sleep wake system mechanisms change and are influenced by these same neurotransmitters
(see Arousal/Sleep Wake Flip Flop section). Since the thalamus forms connections with general vigilance system brain regions, both arousal/sleep wake and general vigilance systems pathways will be involved in vigilance performance. Complex interactions like these may explain why no one vigilance theory can account for vigilance and the vigilance decrement (see the “Theories” section). Figure 23 conceptualizes this complex interaction between the two systems to create an overall conceptual vigilance pathway. Generally speaking, brain system inputs (system input drivers and system inputs) feed into the two brain systems (arousal/sleep wake and general vigilance systems) which interact together to influence vigilance performance.

Figure 23. Overall conceptual vigilance pathway flow diagram
7.0 BLOOD FLOW AND CEREBRAL OXYGEN SATURATION MEASURES

Thus far, this thesis has discussed the main theories and dominant brain regions associated with vigilance performance. Though this information is certainly useful in beginning to understand vigilance and conceptualize the vigilance decrement they do not tell us much about what is actually happening during a vigilance task. What is needed is a physiologic metric of some sort that can reflect vigilance changes, or rather the things that drive vigilance performance. Such metrics are key for model development—the purpose of this thesis. If we can measure what drives vigilance performance we can predict vigilance performance.

In looking at figure 23, one strategy is to use technologies that measure the “brain system inputs” and to treat the “brain systems” as a “black box”7 (Figure 24). This is

7 Engineers (or scientists) often use “black boxes” to represent a system, object, process etcetera. Usually these black boxes have an input and an output, which can be represented mathematically. The black box approach is useful because it does not require
appropriate since all we care about is the input and output of this black box—the physiologic metrics and vigilance performance respectively. This section discusses two of these potential metrics, cerebral blood flow velocity (CBFV) and regional oxygen saturation (rSO$_2$), and the technologies that measure them.

### 7.1 Research Overview

Technologies that measure regional cerebral blood flow (rCBF) or cerebral blood flow velocity (CBFV) and regional oxygen saturation (rSO$_2$) have shed considerable light on hemispheric differences in vigilance research and provide the best means to monitor and quantify cognitive processing resources. Vigilance researchers have particularly used transcranial doppler (TCD) and near-infrared spectroscopy (NIRS) in more recent years because they are relatively cheap, allow subject movement and introduce little to no noise compared to traditional methods such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)(Warm et al., 2008). In general, if the task was sufficiently challenging (Warm et al., 2009) or long enough (Helton et al., 2007), CBFV declined in parallel with vigilance performance and overall regional rSO$_2$ levels increased. Otherwise, these metrics usually did not show much change. Such findings support the notion that a certain degree of task difficulty is required before brain systems involving glucose show any measurable physiological changes (Korol & Gold, 1998 as cited in Warm et al., 2009, p. S89). The TCD and NIRS findings also provide additional evidence for the resource theory and have been used to argue against arousal theory (individuals showed no decline in CBFV with no “work imperative”). TCD has also provided evidence that memory-based tasks (e.g. successive) require more processing.

the user to know all the intricate details of a system. Rather, the user only needs to know the relationship between what comes into and out of that system.
resources than non-memory based tasks. A study by Mayleben et al., (1998) (as cited in Warm et al., 2009) , for example saw higher CBFV levels in successive tasks vs. simultaneous ones (though both showed corresponding decline with the vigilance decrement). The most consistent finding using these technologies has been that cerebral oxygenation and blood flow levels are almost always higher in the right hemisphere. These findings occur whether an actual decrement occurs or not and supports the generally accepted idea that vigilance is primarily right hemisphere dominant. Recent evidence, however, suggests that the left hemisphere plays an increasing role as the vigilance task becomes more difficult. Helton et al. (2010) saw higher rS02 values in the right hemisphere relative to the left during an easy task but equal levels between hemispheres during a hard task.
8.0 INTERVENTIONS

As discussed earlier, vigilance performance/decrement inputs can be measured using physiological metrics such as TCD and rSO₂. The vigilance decrement, however, is often a problem in situations where vigilance performance is needed (see “Problem Statement”). The reader’s next logical question may be therefore, “what actual interventions might exist to prevent, reduce or reverse this vigilance decrement?” Craig, (1984), who has performed a comprehensive review around this question, says this problem can be approached from two directions: “fitting the task to the individual” or by “fitting the individual to the task.” He then discusses how these approaches can be broken up into subcategories shown below:

a) Fitting Task to the Individual
   1. Reduce uncertainties
   2. Motivate or Stimulate the Operator
   3. Moderate Environmental and Other Stresses

b) Fitting the Individual to Task
   1. Selection
   2. Training
   3. Identifying Unacceptable Efficiency Levels

This section summarizes some of Craig’s findings and incorporates more recent literature.
8.1 Task to Individual

8.1.1  *Reduce Uncertainties*

Craig (1984) discusses how uncertainty can be reduced when it is clear what is and what is not a signal, as well as where and when the signal will occur and how many signals to look for. One technique is to provide more than one source of information that describes the same thing. One study by Craig (1984) applied this technique by providing redundant audio and visual information. The result was a 50% improvement across subjects on the detection. More recently, Hitchcock et al. (2003) significantly counteracted the vigilance decrement by giving subjects cues prior to the signal presentation with varying reliabilities. Interestingly, the vigilance decrement was completely absent in the 100% reliability cue condition and CBFV values paralleled performance values for all conditions (40%, 80%, 100% reliability) in the right hemisphere. Unfortunately, in many real-life scenarios it is impossible to exactly know when a signal may appear beforehand, but the research suggests a potential benefit for using probabilistic cueing as an intervention for the vigilance decrement.

8.1.2  *Motivate or Stimulate the Operator*

Clearly, how much a subject is motivated/stimulated impacts their performance and is the essence of the decision criterion in SDT. Motivational factors can range from forms of verbal encouragement to the use of various types of rewards (e.g. monetary) or negative consequences. Performance feedback, both positive and negative (depending on the individual), can also have an effect on subject motivation and result in task performance improvement (Idson & Higgins, 2000). Means of stimulating the subject are often those that influence arousal (see “Arousal Section”) such as drug stimulants (e.g.
caffeine, nicotine, epinephrine and amphetamines) or environmental stressors (e.g. exercise). Lieberman, Tharion, Shukitt-Hale, Speckman, and Tulley, (2002) for example saw significant “improved visual vigilance” and “choice reaction time” in Navy Seals after taking 200 and 300 mg of caffeine following 72 hours of sleep deprivation (see McLellan, Kamimori, Voss, Tate, & Smith, 2005 for a similar study). Caffeine additionally “mitigated many adverse effects of exposure to multiple stressors.” While other motivational factors certainly exist, a comprehensive review of these mechanisms is beyond the scope of this thesis.

8.1.3 Moderate Environmental and other Stressors

Environmental stressors and others that can be modulated include things like temperature, comfort, knowledge of observation, vibration and environmental noise. The stressful nature of the task can also impact performance. Anxiety, for example has been shown to impair cognitive performance (Eysenck, Derakshan, Santos, & Calvo, 2007) though it can also facilitate performance (Eysenck & Calvo, 1992). Those concerned about vigilance performance must therefore ensure that their own subject-interactions and study design reduce subject anxiety as much as possible. For an in depth review of environmental stressors see Hancock (1984).

8.2 Individual to Task

Individual differences, which are inherent in any situation, can significantly influence vigilance performance. Selecting for individuals that are ideal for a vigilance task, therefore, is possible. As discussed in Reinerman-Jones, Matthews, Langheim, and Warm, (2010) and Finomore, Matthews, Shaw, and Warm, (2009), traditional “unidimensional” measures such as personality factors and age are not adequate means of
individual vigilance-task selection. Instead, “multivariate assessment strategies” that combine measures such as CBFV and workload are more appropriate, and have shown promising results.

8.3 A Potential New Intervention—Transcranial Direct Current Stimulation

One potential intervention yet to be applied to vigilance is the use of transcranial direct current stimulation (tDCS). tDCS injects very weak currents (~1-2 mA) into the brain by passing current from anode to cathode electrode(s) placed over the scalp. Since current exists at the cathode, charge or pools of electrons build up underneath the cathode electrode (George & Aston-Jones, 2010). As a result, the anode is conceptualized as injecting “positive” current and the cathode “negative.” Generally (though not always), anodal stimulation increases excitability while cathodal stimulation decreases excitability by increasing and decreasing membrane potentials (i.e. depolarizing and hyperpolarizing) respectively (Nitsche & Paulus, 2000; George & Aston-Jones, 2010). Though tDCS current densities/magnitudes cannot sufficiently elicit actual action potentials they can change the probability of action potential firing (i.e. neuromodulate) (Nitsche, et al, 2008). With tDCS’s ability to increase or decrease membrane excitability, therefore, tDCS can influence cognitive skill sets such as vigilance (see McKinley, Bridges, Walters& Nelson, in review, 2011).

Traditionally, brain stimulation technologies, like tDCS, have been used as therapeutic agents or aids in the medical environment (Wagner, Valero-Cabre, & Pascual-Leone, 2007). For the case of tDCS, researchers have shown therapeutic potential for major depressive and bipolar depressive disorders (Brunoni et al., 2011), Parkinson’s (Benninger et al., 2010), tinnitus (Garin et al., in press; Fregni et al., 2006) and stroke
rehabilitation (Schlaug & Renga, 2008)—though larger studies are needed to determine therapeutic practicality. The “healthy” controls and other studies have shown, however, that tDCS can also be used to enhance cognitive performance in individuals not requiring therapy (see McKinley et al., in review). Given its cognitive enhancement potential, tDCS, therefore, may prove useful as a novel tool in military settings heavily dependent on cognitive processing skill sets such as vigilance.

8.3.1 **Short Term vs. Long Term Effects**

Generally, the mechanisms of tDCS can be divided into short-term and long-term effects. In the short-term, the injection of current raises/lowers the membrane potential of regional neurons. This variance in membrane potential influences voltage-gated ionic channel (e.g. Na+/K+ pump) behavior, which ultimately contributes to membrane excitability changes seen in the short-term (Liebtanz, Nitsche, Tergau, & Paulus, 2002). If tDCS is provided for a sufficient amount of time, however, long-term effects that last for longer periods after stimulation termination appear (Nitsche et al., 2003; Nitsche and Paulus, 2001; Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004). These effects are thought to be analogous to the neuroplastic processes of long-term potentiation (LTP) and long-term depression (LTD). It is thought that potentiation is a result of increased or decreased efficiency of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (or AMPA) receptors at synapses which leads to increased or decreased synaptic strength—LTP and LTD respectively (see Carlson 2010). Since the neuronal synapses have experienced structural changes, physiological and psychological processes tied to these synapses and their neural pathways are also changed. Thus, long-term effects become present after stimulation termination (see McKinley et al., 2011).
8.3.2 Applying tDCS to Vigilance

In the context of vigilance, tDCS might replace/account for lost attentional processing resources (see the “Resource Theory” section) by increasing neural activity in brain regions responsible for vigilance. Additionally, researchers have shown that tDCS can increase rCBF (Lang, et al., 2005) and rSO₂ (Merzagora, et al., 2010) to stimulated regions. Since, depending on the task and brain region, CBFV parallels the vigilance decrement (see the “Blood Flow and Cerebral Oxygen Measures” section), tDCS-induced increased CBFV might effectively counteract or even prevent the vigilance decrement. The McKinley Study investigates this possibility (see chapter 9).
9.0 MCKINLEY STUDY

The data for this thesis was pulled from the McKinley Study described in this section.

9.1 McKinley Study Purpose and Goals

The Air Force Research Laboratory (AFRL) conducted a study to determine the feasibility of using transcranial direct current stimulation (tDCS) as a means to counteract the vigilance decrement. As mentioned in earlier sections both cerebral blood flow velocity (CBFV) and regional cerebral oxygen saturation (rSO₂) have shown relationships to vigilance task performance during vigilance decline. The potential exists, therefore, to use these two “metrics” as a means to monitor and quantify the vigilance decrement. It is the AFRL’s hope that these metrics can be incorporated into a type of physiological feedback vigilance monitoring system that can identify vigilance decline and intervene using tDCS. Specific to this study, the stated research goals were to:

1) Quantify changes in blood flow velocity and/or cerebral oxygen saturation resulting from low level (1 mA) anodal and cathodal tDCS

2) Quantify performance changes in vigilance performance with and without tDCS stimulation

9.2 Experimental Procedure & Design

In the study, 20 “healthy” subjects underwent a 40-minute vigilance task (see section below) and received 10 minute anodal, cathodal and sham stimulation (on separate days) either 10 or 30 minutes into the test run (see table 4). Prior to the actual study, subjects were screened using the 40 minute vigilance task (after two 5 minute practice sessions).
Study participants were then chosen on the condition that they showed a vigilance decline and drop in CBFV during the task. After selection, subjects performed the vigilance task with each condition of stimulation on three separate days in a randomized order.

Subjects took a “Mood Questionnaire” immediately before and after each stimulation and were not permitted to leave until mood levels return to baseline values (prior to vigilance task). All participants provided an informed consent and this procedure was approved by the AFRL Internal Review Board.

Table 4. 2x3 mixed factorial design used in the McKinley Study

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9.3 Vigilance Task

In the vigilance task, subjects are presented with four arrows either pointing generally in a clockwise or counterclockwise direction (see Figure 25). The circle of arrows appear and disappear at a rate of 1000 ms always in the same location at the center of the screen. On infrequent unknown occasions two arrows point towards one another—simulating a potential collision incident. During the 40 minute task subjects look for these collision incidents and indicate a “hit” by depressing the spacebar key. “Hits,” “Misses,” “False-Alarms,” “Correct Rejections” and reaction times are all compiled into an access database for post-processing (see Post-Processing below).

![Figure 25. Image of vigilance task used in the McKinley Study](image)

9.4 Transcranial Direct Current Stimulation

McKinley study researchers chose tDCS as the brain stimulation technology (versus other technologies) for the following reasons:

1) Demonstrated cognitive enhancement and favorable hemodynamic effects
2) Cheaper than other technologies (e.g. transcranial magnetic stimulation)

3) Easier to use in military environments

4) More likely to incorporate into existing technologies and/or systems

As briefly mentioned in the “A Potential New Intervention—Transcranial Direct Current Stimulation” section, researchers have demonstrated cognitive enhancement potential (see McKinley et al., in review) and favorable hemodynamic effects (Lang, et al., 2005; Merzagora, et al., 2010). The technology is also, because of its relative simplicity (simple electrodes and a 9-volt battery), both cheaper and easier to use in military environments. Such specifications are necessary in environments where users may be in motion and require uninhibited interaction with other existing technologies and human systems. Additionally, such specifications make tDCS a likely candidate for incorporation into technologies and/or systems currently being used in the Air Force environment. These findings, along with being noninvasive and with minimal side effects, made tDCS a likely candidate for experimental investigation—hence the initiation of the McKinley Study (see chapter 9).

Since the dlPFC is thought to play a role in vigilance (see the “General Vigilance Systems” section), 1 mA tDCS was provided to both hemispheres. The electrodes were positioned such that one hemisphere saw one polarity while the other hemisphere saw the opposite polarity (e.g. left anodal and right cathodal). Funke (2009), who ran a study using this same task, found a CBFV decline in the left hemisphere but not in the right hemisphere during vigilance performance decline. Consequently, a smaller electrode was always placed over the left dlPFC, regardless of polarity, because it provided a larger and more focal current density. Anodal and cathodal conditions involved a 15 second ramp
up to 1 mA which was maintained for 10 minutes and a 15 second ramp down. To mimic
the momentary “tingling” sensation experienced in the real stimulation conditions the
sham or control condition provided a 15 second ramp up and ramp down at 1 mA to both
cortices.

9.5 Post-Processing

To find percent accuracy a series of visual basic macros divide the total number of
actual “hits” by the total number of possible “hits” every 10 minutes. The first 10
minute percent accuracy value was treated as a baseline and the remaining three 10
minute percent accuracy values were scaled to that baseline to form “%change” values.
A similar procedure is used for the TCD and NIRS data. Instead of using accuracy
values averages of absolute readings are taken every 10 minutes and normalized using
the average for the first 10 minutes.

Raw and averaged physiological and performance data sets were organized by
separate Excel spreadsheets. A “physiological summary” sheet provided a complied
version of the scaled TCD and oximeter data measures (averaged every 10 minutes) for,
while a “performance summary” sheet provided the same for %Hits, %Change and
%RT.

9.6 Equipment

9.6.1 Stimulator

The U.S. Food and Drug Administration (FDA) approved MagStim DC (direct
current) stimulator (Magstim Company Limited; Whitland, UK) provides the tDCS in
this study figure 26. Two rubberized electrode pads inserted in saline-soaked sponge
sleeves provide the electrical stimulation. The DC stimulator has a feature that adjusts the impedance values (between electrode and skin) to maintain the specified current value. If impedance values were too high the stimulator automatically shut off and the test run was scrapped.

Figure 26. Image of the tDCS stimulator used in the McKinley Study

9.6.2 Transcranial Doppler (TCD)

CBFV was continuously monitored using a FDA approved SONARA/tek (Conshohocken, PA) TCD unit figure 27. A 2 MHz probe was used to monitor blood flow in the middle cerebral artery (MCA) by placing it over the transtemporal window. Since the MCA carries 80% of the blood within each cerebral hemisphere (Tripp & Warm, 2007) and its diameter stays relatively constant during remote changes in vascular activity (Duschek and Schandry 2003 from Tripp & Warm, 2007, p. 84), it serves as an ideal area for monitoring changes in metabolic resources (Stroobant & Vingerhoets, 2000). The TCD device applied a 300Hz filter with a sweep time of 4 seconds.
9.6.3 **Cerebral Oximeter**

An INVOS 5100C cerebral oximeter (Somanetics; Troy, MI) was used to collect rSO$_2$ values during the study (Figure 28). The cerebral oximeter uses two sensor patches placed over the forehead that each contain an infrared light (730nm and 810nm) emitting LED and two photodetectors. The first photodetector (located 30 mm from the light source) detects infrared light that passes through surface skin and skull while the second (located 40 mm from the light source) detects light that passes through the cerebral cortex. rSO$_2$ values are calculated by taking the difference between the two photodetector values every four seconds. Hongo, Kobayashi, Okudera, Hokama, and Nakagawa (1995) have validated INVOS cerebral oximeter values and the device has been approved by the FDA.
Figure 28. (Left) Image of cerebral oximeters (Right) Image of experimental setup including cerebral oximeters
10.0 RESEARCH APPROACH

This thesis’s research approach was directed toward addressing the questions presented in the “Purpose of Thesis” section. The questions are restated below.

1) How well can the averaged normalized vigilance performance (VP*avg.)—both during and after tDCS, be predicted using the average (across subjects) of any if not all of the following metrics: right and left hemispheric cerebral blood flow velocity (CBFV), regional cerebral oxygen saturation (rSO2), heart rate (HR) and the stimulation parameters (e.g. location and polarity) used in the McKinley Study (see chapter 9) ?

2) Which of these metrics (or input variables) are key in predicting VP*avg. (during and after tDCS) and hence tDCS-vigilance effects for both real and control stimulation conditions (anodal and sham respectively)?

3) How well can VP*avg. be used to predict vigilance performance (% hits) in individual subjects—both during and after tDCS for both real and control stimulation conditions?

10.1 Delimitation Selection

It was determined that examining the 10 minute anodal stimulation condition of the McKinley Study (chapter 9) would best meet the needs described in the “Purpose of Thesis” section. This delimitation and the rationale behind it are described in detail below.
10.1.1 **10 Minute Condition**

As discussed in the McKinley Study section of this thesis (see chapter 9), study participants received 10-minute stimulation 10 minutes (10 Minute Condition) or 30 minutes (30 Minute Condition) into the 40 minute vigilance task (see Figure 29). As depicted in figure 29, the McKinley Study takes averages of vigilance performance (%hits) every ten minutes and normalizes them by dividing by the first 10 minute average (i.e. baseline performance)—creating four data points for a total of 40 minutes. Since the task is 40 minutes long and the stimulation lasts for 10 minutes, the 30 Minute Stimulation Condition does not allow for tDCS aftereffects (see Figure 29b). The 10 Minute Condition, however, allows for the establishment of a baseline (prior to stimulation), provides stimulation early in the task, and has 20 minutes of no stimulation (see Figure 29a) for a vigilance decrement to occur. Such a setup is ideal for meeting the goal/purpose of this thesis—to develop a model capable of predicting vigilance performance effects during stimulation and after stimulation.

![Figure 29. Compares tDCS stimulation conditions used in the McKinley Study](image)

Figure 29. Compares tDCS stimulation conditions used in the McKinley Study
10.1.2 *Anodal Stimulation Condition*

Funke (2009), whose vigilance task is identical to the task used in the McKinley Study (chapter 9), showed a decline in cerebral blood flow velocity (CBFV) in the left hemisphere while the right hemisphere remained constant. Since the left hemisphere is the only measurable physiological signal that changed (in this case declined) as subjects experienced a vigilance decrement, it is reasonable to assume that the left hemisphere primarily governs the vigilance decrement for this task. Recall that tDCS works by passing current from a cathode to an anode through the brain (i.e. the brain completes the circuit between a positive and negative pole). Recall also that anodal tDCS generally increases neuronal excitability and CBFV at the electrode site, while cathodal tDCS does the opposite (see “A Potential New Intervention—Transcranial Direct Current Stimulation” section). Therefore, it is plausible that anodal tDCS applied to the left hemisphere, which should theoretically result in increased excitability and CBFV, should by resource and arousal theory, result in improved vigilance performance (i.e. mitigate the vigilance decrement).

The McKinley Study (chapter 9) used two electrode configurations. In the first configuration, termed here as “Anodal Right,” the anode electrode is placed over the right hemisphere while the cathode is placed over the left hemisphere (Figure 30). Theoretically, this would mean that the right hemisphere is having increased neuronal activity and blood flow while the left hemisphere is seeing the exact opposite. If the assumption that the vigilance decrement is primarily controlled by the left hemisphere for this task is correct, the “Anodal Right” configuration should lead to a larger vigilance
decrement. The second configuration, “Anodal Left,” which is the reverse setup of “Anodal Right,” should, however, reduce the vigilance decrement (i.e. improve vigilance)—the goal of the McKinley Study (see chapter 9). In this case, the left hemisphere should have an increase in excitability and CBFV, because it is under the anode electrode. Since the aim of this thesis is to develop a model that might one day aid in predicting positive tDCS-effects (versus negative effects) on vigilance performance the “Anodal Left” condition was chosen as the data set for modeling.

![Diagram of 10-Minute Stimulation Condition](image)

**Figure 30.** Thesis aim within the 10 minute stimulation condition experimental setup

### 10.2 Methodology

#### 10.2.1 Model Output ($VP^*$)

As discussed, the aim of this thesis was to develop a model that predicted the average %hits/baseline ratios ($VP^*_\text{average}$) during the McKinley Study (see chapter 9) vigilance
task using the McKinley study data. Figure 31 depicts the process in creating this value. A 10-minute baseline was first created for each subject by averaging the values over that time period (Figure 31a). The percent accuracy values were then divided by this baseline to create $VP^*$ for each subject (Figure 31b). For later regression fitting, these $VP^*$ values were then averaged together to make a single %hits/baseline plot across all subjects (Figure 31c).

Figure 31. Flow Diagram depicting performance relative to baseline calculation
To determine whether $VP^*$ in the anodal and sham conditions differed significantly in the McKinley Study, a one-way analysis of variance (ANOVA) was performed with stimulation condition (anodal and sham) as the main effect and each subject ($N=9$) blocked.

10.2.2 Model Input Variables

As mentioned in the “Purpose of Thesis” section, the modeling development process begins with a starting model that contains all potential metrics or input values collected during the vigilance task in the McKinley Study. These metrics include:

1) Normalized Right Cerebral Blood Flow Velocity ($CBFV_R^*$)
2) Normalized Left Cerebral Blood Flow Velocity ($CBFV_L^*$)
3) Normalized Right Cerebral Blood Flow Velocity ($rSO_2R^*$)
4) Normalized Right Cerebral Blood Flow Velocity ($rSO_2L^*$)
5) Normalized Heart Rate (HR*)

6) tDCS Amplitude (A)

7) time (t)

“Normalized” metrics (those with “*”) are those that were divided by their baseline value (e.g. VP* = %hits/baseline) in equation 1. As previously discussed, CBFV and HR are measured using Transcranial Doppler Sonography (TCD) and rSO₂ measured using a cerebral oximeter (attached to the frontal lobes) continuously throughout the entire 40-minute vigilance task. “A,” the tDCS current amplitude, starts at 0 mA and ramps up to 1 mA in 15 seconds (see chapter 9 for more details) ⁸.

The reader should recall that the normalized metrics were collected continuously over the course of the 40-minute vigilance task for each subject. Thus, several 40-minute data sets existed for each metric. For model development these data sets were averaged together to make one data set (much like VP* in Figure 31c is an average of normalized performance values). Averaging is advantageous in this case because it helps remove sources of variability between subjects that take away from the true relationship between the metrics and the output variable VP*. “A” on the other hand did not need to be averaged across subjects as its profile (how tDCS current changes with time) was exactly the same for each subject.

---

⁸ An ampere (in this case a milliampere; mA) is the SI unit of current.
10.2.3 Starting Model

![Model Flow Diagram—Starting Model](image)

All regression modeling was performed using JMP 9.02 using an “all possible combinations” approach. The algorithm is advantageous because it accounts for the subset biases that might occur when performing forward, backwards or stepwise regression by developing regressors using input variables in every possible order (i.e. it examines every possible regressor subset) (Ryan, 2007).

To start, JMP asks that an output variable is selected (in this case %hits/baseline) and model effects are selected (figure 34). The model effects are the initial input variables that JMP considers when performing the regression analysis. All possible regression was started off with three separate combinations of model effects which each generated a lengthy list of possible models. The first combination used each metric without any interactions (e.g. CBFV\textsubscript{L}*, CBFV\textsubscript{R}*, rSO\textsubscript{2,L}* etc.). To generate the second combination the factorial to the second degree JMP macro was used, which created all possible combinations of the metrics crossed with each other (e.g. CBFV\textsubscript{L}* x CBFV\textsubscript{R}* , rSO\textsubscript{2,L}* x HR*\textsubscript{avg}, CBFV\textsubscript{R}* x A etc.). This combination was created to address the hypotheses.
discussed in section 10.3. Second order model effects were created in the third combination using the “polynomial” macro in JMP (e.g. \([\text{CBFV}_L^*]^2\), \([t]^2\), \([\text{rSO}_2,R^*]^2\), etc.)

Figure 34. JMP print-screen of model development page
10.2.4 *Model Selection*

Before a model could be “considered” it had to pass a set of selection criterion in the model selection phase (Figure 35). These included:

1) Coefficient of determination ($R^2$) above .70

2) All model terms had to be statistically significant (p-value< 0.05)

3) A variance inflation factor (VIF) less than 5 (preferably lower)

The equation for $R^2$ is shown below. This commonly used goodness-of-fit measure represents the variability accounted for by the predictor or input variables used in the model (Ryan, 2007). The author selected the “above .70” $R^2$ model requirement because models with values below this threshold would likely not account for enough variance to be useful for this thesis’s purposes. JMP uses a t-test to determine statistical significance of the each parameter estimate (portion of model equation using the input variable). If the resultant p-value was below 0.05 the parameter and corresponding model term was considered statistically significant. The VIF was calculated for models with more than one term that met the first two criteria listed above. The VIF provides a measure of
multi-collinearity in the statistical model. Though no set value exists, the commonly used “rule of 5,” was used to distinguish between models with high and low multi-collinearity (O’Brien, 2007).

Table 5. Term Definitions

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Total number of observations (i.e. sample size)</td>
</tr>
<tr>
<td>p</td>
<td>Total number of regressors</td>
</tr>
<tr>
<td>$y_i$</td>
<td>Observation(s)</td>
</tr>
<tr>
<td>$\bar{y}$</td>
<td>The mean of the observed data</td>
</tr>
<tr>
<td>$\hat{y}$</td>
<td>Predicted output value (from model)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Regressor coefficient</td>
</tr>
<tr>
<td>X</td>
<td>Input Variable</td>
</tr>
</tbody>
</table>

\[
\bar{y} = \frac{1}{n} \sum_{i=1}^{n} y_i \quad \text{(Equation 7)}
\]

\[
\hat{y} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p \quad \text{(Equation 8)}
\]

\[
R^2 = \frac{\sum_{i=1}^{n} (y_i - \bar{y})^2}{\sum_{i=1}^{n} (y_i - \hat{y})^2} \quad \text{(Equation 9)}
\]

\[
VIF = \frac{1}{1 - R^2} \quad \text{(Equation 10)}
\]
10.2.5 *Model Consideration*

Models that met the criteria mentioned in the prior section were subject to another set of tests to determine the optimal model in Model Consideration phase (Figure 36). VP* was determined for each subject using their physiological data for each model under consideration. Percent error (equation 11) was calculated for each predicted data point for each subject. Additionally, $R^2_{\text{adjusted}}$ (equation 12) values were calculated for each model. In multiple regression, the addition of a new term increases the $R^2$ value (i.e. it becomes inflated). This $R^2$ inflation can lead to biased answers that result in a less than optimal model. An alternative is to use $R^2_{\text{adjusted}}$, which has the ability to decrease as the number of regressors (input variables’ constants) increases (Ryan, 2007) and therefore accounts for inflation. The model with the best mean %error and $R^2_{\text{adjusted}}$ was selected as the optimal model.

$$\text{%error} = \frac{|\text{actual} - \text{predicted}|}{\text{predicted}}$$  \hspace{1cm} (Equation 11)

$$R^2_{\text{adjusted}} = 1 - (1 - R^2) \frac{n-1}{n-p-1}$$  \hspace{1cm} (Equation 12)
10.2.6 **Optimal Model**

After the optimal model was selected using the techniques described during model consideration, the assumptions under which it was created needed to be tested for—namely the assumptions of linear regression (Figure 37). These assumptions included that the residuals were normally distributed and independent with a mean of zero and a constant variance (Ryan, 2007). Normality and independence assumptions were tested using the Shapiro-Wilks and Durbin-Watson tests. The residual mean value was also calculated in JMP and constant variance was checked by examining a plot of the residuals versus VP*.

10.2.6.1 **Anodal vs. Sham Conditions**

Up to this point in the analysis the approaches used were directed for the anodal stimulation condition since the primary thesis objective was to create a model optimized to this condition. The model, however, would not be useful if it could not be applied in scenarios when subjects were not being stimulated. In these scenarios prior brain stimulation might change how the metric (e.g. blood flow) relates to vigilance.
performance—which would consequently reduce the predicting power of the model (or even make it completely invalid). For example, if $VP^* = 2(CBFV) + 5$ before stimulation it might change to $VP^* = -40(CBFV) + 29$ after stimulation—a relationship the user could not know in real-time. Furthermore, the perception/belief of being stimulated (even in cases with no stimulation) could have physiological effects alone that might make the model invalid. To examine these possibilities the model developed under the anodal stimulation condition was applied to the sham stimulation data. Recall that the sham condition used a 1 mA current amplitude for 30 seconds to mimic the sensations of the anodal stimulation condition (1 mA for 10 minutes). Given these parameters the sham condition physiological effects were considered negligible compared to the anodal condition, but provided a psychological backdrop equivalent to the anodal stimulation condition. These facts and assumptions made model testing in the sham condition appropriate.

Optimal model metric(s) time series plots were first compared with a $VP^*$ time series plot for both stimulated and sham conditions to determine and discuss a relationships that could be determined visually. Best fit lines were then fitted (and equations displayed) to anodal and sham $VP^*$ versus optimal model metric(s) to compare the quantitative relationships these metrics had in both stimulation conditions (see example Figure 38).
Figure 38. Example showing how the relationship between vigilance performance and the metric(s) used in the model are determined

The predictive power of the model was then demonstrated by plotting the actual and predicted VP* values and actual performance (%hits) calculated from these values for both the anodal and sham stimulation conditions (recall that VP* multiplied by baseline equals actual performance; equation 2). To assess the model goodness-of-fit in both stimulation conditions, actual performance was plotted against model predicted performance. Since the slope of this best-fit line indicated how closely equivalent the predicted values were to the actual ones (a slope of “1” indicated a perfect equivalency) the slope was used to determine a quantitative measure goodness-of-fit. To test the model’s robustness for each subject across time, %errors were calculated for model’s ability to predict % hits were found for both the anodal and sham conditions.

10.3 Hypothesis

Before any data analysis was performed, hypotheses were made about the three question stated in the “Purpose of Thesis” section. The hypotheses and rationales behind them are described below.
10.3.1 **Question 1**

How well can the average performance to baseline ratio (performance/baseline)—both during and after tDCS, be predicted using the average (across subjects) of any if not all of the following metrics: right and left hemispheric cerebral blood flow velocity (CBFV), regional cerebral oxygen saturation (rSO2), heart rate (HR) and the stimulation parameters (e.g. location and polarity) used in the McKinley Study?

To the author’s knowledge, no one had attempted to fit vigilance performance relative to baseline performance, both before and after tDCS, using the metrics described in the McKinley Study. Hypothesizing plausible goodness-of-fit metric ranges was therefore difficult. Work by some research groups who tried modeling vigilance performance generally, however, suggested that metrics like CBFV, might prove useful in predicting vigilance performance. Both Matthews et al. (2010) and Reinerman-Jones et al. (2010) show statistically significant positive correlations between CBFV and A’\(^9\) (perceptual sensitivity measure; see SDT section). These correlations, for both studies, became increasingly significant as the vigilance task progressed. Since changes in perceptual sensitivity have been shown to play a large role in the vigilance decrement (depending on the task) it was assumed that these metrics might also correlate to blood flow velocity metrics. Aside from studies attempting to use models, several studies looking at vigilance generally have shown positive correlations between vigilance performance and blood flow velocity (see “Blood Flow and Cerebral Oxygen Saturation Measures” section for a review). Therefore, it was hypothesized that the model should show at least some partial success in predicting vigilance performance.

\(^9\) A’ is the nonparametric equivalent of d’, which is intended for parametric distributions.
10.3.2 **Question 2**

*Which of these metrics (or input variables) are key in predicting the vigilance performance to baseline ratio (during and after tDCS) and hence tDCS-vigilance effects?*

While very little literature existed that could support a hypothesis of the potential effectiveness of the model quite a lot of literature existed that talked about physiologic metrics generally. This allowed for reasonable key input variable hypotheses. Table 6 highlights the hypothesized key input variables/metrics that were thought would remain or be removed when selecting an optimal model. These included $\text{CBF}_{V_L}, \text{CBF}_{V_R} \times \text{CBF}_{V_L}$, and $A$. In Funke (2009) (remember he used the same task) $\text{CBF}_{V_L}$ showed a decrement in sequence with the vigilance decrement, while $\text{CBF}_{V_R}$ stayed relatively constant. Such findings would suggest that any loss of resources throughout the vigilance task is primarily reflected in the left hemisphere, but not in the right. Therefore, it was hypothesized that $\text{CBF}_{V_L}$ would remain in the model while $\text{CBF}_{V_R}$ would be removed. As the reader may recall, however, a large body of literature has shown that overall vigilance (which may be governed differently than the vigilance decrement itself) is generally right hemisphere dominant but may become de-lateralized (i.e. show activity in both hemispheres) as the task difficulty increases (see “General Vigilance Systems” and “Blood Flow and Cerebral Oxygen Saturation Measures” Sections). In this case, it may be that the two hemispheres interact in some way to produce vigilance decrement effects. Changes in $\text{CBF}_{V_L}$ would still be primarily responsible for the vigilance decrement in this task, but the degree of its impact influenced by the $\text{CBF}_{V_R}$ level in the right

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10 An example of an interaction term
hemisphere. It was hypothesized, therefore, that an interaction term (CBFV_R x CBFV_L) would exist between blood flow velocities in both hemispheres.

Table 6. Summarizes the hypotheses for the metrics and their corresponding explanations in regards to the second question posed in the “Proposal of Thesis” section

<table>
<thead>
<tr>
<th>Metric</th>
<th>$\mu_o=$not included in optimal model</th>
<th>$\mu_1 \neq \mu_o$ (included)</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBFV_R</td>
<td>$\mu_0$</td>
<td></td>
<td>Funke 2009 found that this did not change during the vigilance task</td>
</tr>
<tr>
<td>CBFV_L</td>
<td>$\mu_1$</td>
<td></td>
<td>Funke 2009 found that this showed a decrement in sequence with the vigilance decrement</td>
</tr>
<tr>
<td>CBFV_R x CBFV_L</td>
<td>$\mu_1$</td>
<td></td>
<td>Literature suggests that the two hemispheres interact when vigilance tasks are sufficiently difficult</td>
</tr>
<tr>
<td>rSO_2,R</td>
<td>$\mu_o$</td>
<td></td>
<td>Did not change over time in Funke 2009</td>
</tr>
<tr>
<td>rSO_2,L</td>
<td>$\mu_o$</td>
<td></td>
<td>Did not change over time in Funke 2009</td>
</tr>
<tr>
<td>HR</td>
<td>$\mu_o$</td>
<td></td>
<td>Literature suggests that HR shows a lot of variability between subjects on tasks</td>
</tr>
<tr>
<td>yr</td>
<td>$\mu_o$</td>
<td></td>
<td>Literature shows that age did not make a difference in these types of sustained attention tasks</td>
</tr>
<tr>
<td>A</td>
<td>$\mu_1$</td>
<td></td>
<td>Anodal stimulation is shown to increase blood flow, oxygen saturation and neuronal excitability at the stimulation site</td>
</tr>
</tbody>
</table>

Finally, it is known that anodal stimulation could increase blood flow, oxygen saturation and neuronal excitability at the stimulation site (see “Short Term vs. Long Term Effects” section). The blood flow and oxygen saturation changes induced by tDCS would largely be captured by the CBFV model input terms. It was more likely thought, however, that additional physiological effects (not accounted for by the CBFV terms)
exist. Therefore, it was hypothesized that “A,” which represents any other tDCS effects not accounted for by the other metrics, would also be important in predicting vigilance performance. The remaining metrics, rSO$_2$R, rSO$_2$L, HR and yr were hypothesized as not important in the optimal model because literature has shown that they either do not vary with time (see “Background” section and Ballard, 1996) or showed too much variability between subjects in the task.

10.3.3 Question 3

How well can this predicted performance to baseline ratio be used to predict vigilance performance in individual subjects—both during and after tDCS?

The success of predicting individual vigilance performance depends on how well VP* can be predicted. This is different from the average of these metrics (between subjects), for which some of the between-subject variability is reduced (Figure 39a). Recall that the regression model is fit to an average of all the metric data sets for each subject (see “Input Variables” section). The model, therefore, is in a way optimized to the averaged data set. Since the model is optimized to the average data set, it was thought that individual VP* would not fit the data as strongly (compared to predicting the VP*) because of the inherent variability introduced by the subject (compare Figure 39a and Figure 39b).
It also was thought that the proposed metrics would likely not account for all the sources of variability between individuals. For example, task engagement in addition to CBFV, is often cited as having statistically significant correlations with vigilance performance (Matthews et al., 2010; Reinerman-Jones et al., 2010; Finomore et al., 2009). Several other sources of variability will exist between individuals, such as personality type, amount of hours slept and food levels. This is not to mention the variability factors, such as head circumference and brain tissue morphology, that influence tDCS-effects. It was suspected, therefore, that the model’s ability to predict the individual VP* (and hence individual performance) would be less than the model’s ability to predict VP* of the averaged dataset. It was hypothesized, however, that the model would provide a good sense of the general trend of an individual’s performance. A model like this would still be useful because it provided an approximation an individual’s performance level at the end of the vigilance task.
11.0 RESULTS

11.1 Anodal Stimulation Performance Results

The data presented in the McKinley Study section (see chapter 9) was preliminary and therefore did not include the entire subject pool. Since this thesis’s modeling approach centered around the 10 minute anodal stimulation condition of the McKinley Study it was necessary to compare the anodal and sham conditions with the entire data set. Figure 40 depicts these two stimulation conditions and shows that anodal stimulation successfully mitigated the vigilance decrement over the course of the 40 minute task.

![Anodal vs. Sham Stimulation](Figure 40. Plot depicting anodal versus sham (control) stimulation conditions with error bars as standard error. Anodal and sham stimulation began 10 minutes into the task.)
To test if the anodal and sham conditions were statistically significant an ANOVA with subjects as a blocking variable was performed. As highlighted below, performance under the anodal stimulation condition was statistically higher than that under sham stimulation (p=0.0004*). ANOVA analysis also shows that a statistical difference exists between at least one of the subjects.
11.2 Regression Analysis

JMP all possible regression analysis produced well over 200 regression model candidates. These models were dwindled down to the most appropriate using the methodologies described in the methods section above. Table 9 describes models that address the hypothesized included model terms, while table 10 represents the select few models that remained after applying the model consideration criteria described in the methods section.

The below table provides the physiological metric, its corresponding hypothesis regarding its inclusion in the optimal model and the structure of the terms used in the actual regression model. Table 9 also provides $R^2_{\text{adjusted}}$ and p-values\(^{11}\) for models of interest (in regards to fit to the average of all the subject data sets). In some cases, small $R^2$ values resulted in negative $R^2_{\text{adjusted}}$ values (recall that $R^2$ makes up $R^2_{\text{adjusted}}$; see equation 12). $R^2$ values were also provided in parenthesis when these negative values appeared. P-values are only provided in cases when these $R^2_{\text{adjusted}}$ values are above .70 (highlighted).

\(^{11}\) When prompted JMP will perform an ANOVA (including a t-test) using the terms or “parameter estimates” of interest. It is from this analysis that the p-values were derived.
<table>
<thead>
<tr>
<th>Metric</th>
<th>$\mu_0=\text{not included in optimal model } \mu_1 \neq \mu_0 \ (\text{included})$</th>
<th>Actual Terms</th>
<th>$R^2_{\text{adjusted}}$ ($R^2$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBFVR</td>
<td>$\mu_0$</td>
<td>CBFVR</td>
<td>0.501 (0.667)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CBFVR-1)$^2$</td>
<td>-0.407 (0.062)</td>
<td></td>
</tr>
<tr>
<td>CBFVL</td>
<td>$\mu_1$</td>
<td>CBFVL</td>
<td>0.957 (0.971)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CBFVL-1)$^2$</td>
<td>0.669</td>
<td></td>
</tr>
<tr>
<td>CBFVR $\times$ CBFVL</td>
<td>$\mu_1$</td>
<td>(CBFVL-1)(CBFVR-1)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>rSO2,R</td>
<td>$\mu_0$</td>
<td>rSO2,R</td>
<td>-0.245 (.170)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(rSO2,R-1)$^2$</td>
<td>-0.0066 (0.329)</td>
<td></td>
</tr>
<tr>
<td>rSO2,L</td>
<td>$\mu_0$</td>
<td>rSO2,L</td>
<td>-0.1558 (.230)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(rSO2,L-1)$^2$</td>
<td>-.264 (.158)</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>$\mu_0$</td>
<td>HR</td>
<td>(0.509)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(HR-1)$^2$</td>
<td>0.967 (0.978)</td>
<td>0.011</td>
</tr>
<tr>
<td>A</td>
<td>$\mu_1$</td>
<td>A</td>
<td>0.847 (0.898)</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(A-0.3)$^2$</td>
<td>0.847 (0.898)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

* “Yr” was not included because absolute age does not change with time

Most of the metrics hypothesized to be in the optimal model—except “CBFVR $\times$ CBFVL”, had high $R^2_{\text{adjusted}}$ values and statistical significance. Conversely, most of the metrics that were hypothesized to not be included in the model had low $R^2_{\text{adjusted}}$ values. This was the case except for an unexpected “(HR-1)$^2$” term which had an $R^2_{\text{adjusted}}$ and p-value of 0.967 and 0.011 respectively.
Table 10 summarizes all of the models considered for optimal model designation. It provides the model term and corresponding $R^2_{\text{adj}}$ as in table 9. Additionally, table 10 provides a VIF for models with more than one term and the actual equation used to predict the averaged-across-subjects VP* value. To test the models’ strength, the model was used to predict the VP* for each subject. A standard error was calculated, by comparing the predicted and actual values for each individual. The “%errorAvg” value in table 10 represents the average and standard deviation of these standard errors for the last 30 minutes of the vigilance task (recall the first 10 minutes of the vigilance task is a baseline).

<table>
<thead>
<tr>
<th>Model Terms</th>
<th>$R^2_{\text{adj}}$</th>
<th>VIF</th>
<th>%Hits/Baseline=</th>
<th>%ErrorAvg$^{12}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(rSO$_2$,R)$^1_1$)(A-0.3)</td>
<td>0.903</td>
<td>N/A</td>
<td>8.2<a href="A-0.3">(rSO$_2$,R)$^1_1$</a>]+1.0</td>
<td>10.24 ± .07</td>
</tr>
<tr>
<td>CBFV$_L$</td>
<td>0.957</td>
<td>N/A</td>
<td>3.9(CBFV$_L$)-2.9</td>
<td>13.36 ± 0.09</td>
</tr>
<tr>
<td>(HR-1)(A-0.3)</td>
<td>0.961</td>
<td>N/A</td>
<td>-4.6 [(HR-1)(A-0.3)]+1.0</td>
<td>13.40 ± 0.04</td>
</tr>
<tr>
<td>(CBFV$_L$-1)(A -.25)</td>
<td>0.754</td>
<td>N/A</td>
<td>7.3(CBFV$_L$-1)(A -.25)+1.0</td>
<td>17.91 ± 0.13</td>
</tr>
<tr>
<td>CBFV$_R$.[(rSO$_2$,L) - 1] *(rSO$_2$,R) - 1)</td>
<td>0.995</td>
<td>1.165</td>
<td>-219.7[(rSO$_2$,L) - 1] *(rSO$_2$,R) - 1)+1.1(CBFV$_R$)-0.1</td>
<td>23.80 ± 0.36</td>
</tr>
<tr>
<td>(HR-1)$^2$</td>
<td>0.967</td>
<td>N/A</td>
<td>202.5(HR-1)$^2$+1.0</td>
<td>25.27 ± 0.19</td>
</tr>
<tr>
<td>(CBFV$_L$-1)(HR -1)</td>
<td>0.847</td>
<td>N/A</td>
<td>-298.2(CBFV$_L$-1)(HR -1)+1.0</td>
<td>26.46 ± 0.32</td>
</tr>
<tr>
<td>(CBFV$_L$-1)(rSO$_2$,R -1)</td>
<td>0.835</td>
<td>N/A</td>
<td>540.4[(CBFV$_L$-1)(rSO$_2$,R -1)]+1.0</td>
<td>59.11 ± 1.06</td>
</tr>
<tr>
<td>(CBFV$_L$-1)$^2$, rSO$_2$,L</td>
<td>0.998</td>
<td>1</td>
<td>491.9(CBFV$_L$-1)$^2$+1.3(rSO$_2$,L)+2.3</td>
<td>60.98 ± 0.63</td>
</tr>
<tr>
<td>(CBFV$_L$-1)$^2$, (rSO$_2$,L)-1)</td>
<td>0.993</td>
<td>2.558</td>
<td>821.8(CBFV$_L$- 1)$^2$+299.3(rSO$_2$,L)-1$^2$+1.0</td>
<td>121.51 ± 1.26</td>
</tr>
</tbody>
</table>

* Time, which was factored into all the above models, did not show any statistical significance in models with R values above .70 (see Appendix)

$^{12}$ Note: This error represents the average of the average error for each subject for the last 30 minutes of the task.
Considered models are ordered from the lowest to lowest average percent error. The “(rSO_{2,R}-1.)(A-0.3)” model had the highest average percent error. Since “A” is zero for the majority of the task, the model simplifies to its y-intercept (in this case 1) for the majority of the task. This explains why the model best fits the anodal condition—anodal stimulation essentially removes the vigilance decrement, in this case, and makes performance constant. In cases, when the effects of tDCS are not present, however this model is not ideal since vigilance performance normally declines with time. As result, CBFV_{L}, which appears to follow vigilance performance even when no stimulation is present, was selected as the optimal model. The CBFV_{L} model accounts for about 96% of the variability present in the average VP* for all subjects. When using individual CBFV_{L} to predict individual VP*, the model has an average percent error of 13.36 ± 0.09.

11.2.1 Assumptions of Linear Regression

Before the CBFV_{L} can be considered a valid model the assumptions under which it was created must be checked (i.e. the assumptions of linear regression). These assumptions included that the residuals were normally distributed, independent, with a mean of zero and a variance that was constant for each error term. JMP was used to test for these assumptions by applying the Shapiro-Wilks (for normality), Durbin-Watson (for independence) the mean of the residuals (for the mean assumption) and a plot of the residuals versus the predicted (or fitted) values (for the constant variance assumption). The results of this analysis are summarized in table 11 below.
Table 11. Testing for the assumptions of linear regression

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Normality</th>
<th>Independence</th>
<th>Mean=0</th>
<th>Constant Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistic</td>
<td>W=.984</td>
<td>DW=1.874</td>
<td>µ=-1.39^{-16}</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.9233</td>
<td>0.5192</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>H₀</td>
<td>Normally distributed</td>
<td>Errors are uncorrelated</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>H₁</td>
<td>Not normally distributed</td>
<td>Errors are correlated</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Conclusion</td>
<td>Fail to reject the null hypothesis; normally distributed</td>
<td>Fail to reject the null hypothesis; residuals are independent</td>
<td>Mean =0</td>
<td>Values are within 2/1000’s of each other above and below the 0-axis. Therefore, the variance of the residuals is considered constant.</td>
</tr>
<tr>
<td>Assumption met?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*"W" is the test statistic Shapiro-Wilks Test while “DW” is the test statistic for the Durbin-Watson Test

The p-values for the Shapiro-Wilks and Durbin-Watson tests were far greater than .05, which says that we should reject the null hypotheses. In these cases this means that the residuals were normally distributed, uncorrelated and therefore meet the first two stated assumptions of linear regression. The calculated mean was -1.39^{-16}, which is essentially zero—that is, zero. Therefore, the assumption of a residual mean of zero was also met. A visual...
inspection depicted in the “constant variance” reveals no obvious patterns or trends—
therefore the assumption of constant variance was also met.

11.3 The Left Cerebral Blood Flow Velocity Model: Anodal vs. Sham Conditions

Excel was used to make the following plots to illustrate the relationship CBFV_L has
with the anodal and sham stimulation condition (Figure 42). The plot in the upper left
(Figure 42a) illustrates the actual averaged VP*'s across subjects for both the anodal and
sham stimulation conditions. The other two plots illustrate the averaged CBFV_L* across
all subjects for both stimulation conditions. The plot in the top right (Figure 42b) has a y-
axis that is scaled the same as the VP* plot while the plot in the bottom left (Figure 42c)
has a y-axis with a minimized range.
Figure 42. (a) Plot of normalized vigilance performance (VP*) as a function of time for the anodal and sham stimulation conditions. (b) Plot of normalized CBFV_L as a function of time for both anodal and sham conditions. (c) Equivalent to plot b except the y-axis has a smaller range.

Figure 43 depicts plots of the average VP* as a function of the average CBFV_L* data for the anodal and sham conditions. A linear model is fit to both stimulation conditions and the corresponding equation displayed. The reader should note that the linear model for the anodal stimulation condition is the same as the one produced from all possible regression (see table 10).
11.4 Predicting Performance Using the Left Cerebral Blood Flow Velocity Model

Figure 44 shows how well CBFVₐ model outputs match actual data. Figure 44a compares the real anodal stimulation and the predicted anodal stimulation as well as the real sham and predicted performance coefficients (Equation 13) using the corresponding equations depicted in Figure 43. Figure 44b similarly illustrates the predicting power of actual performance (%hits) by multiplying the 10-minute %hits baseline by the coefficients (VP*) (see Equation 14).

\[
VP^* = \frac{\text{%Hits}}{\text{Baseline}} \quad \text{(Equation 13)}
\]

\[
VP = VP^* (\text{Baseline}) = \text{%Hits} \quad \text{(Equation 14)}
\]
Figure 44. (a) Is a plot of actual and predicted VP* (remember VP* equals %hits divided by a 10 minute baseline). (b) Is a plot of actual and predicted VP (this is equal to VP* multiplied by the 10 minute baseline).

Figure 45 shows plots of the actual %hits versus the %hits predicted by the CBFV\textsubscript{L} model. The top plot depicts this relationship for both the anodal and sham stimulation conditions while the bottom plot depicts these relationships and provide a best-fit line and equation for each condition. For the anodal condition the slope of the best-fit line is 0.86 while the slope for the sham condition is 0.93.
Table 12 provides a sense of model robustness by displaying its ability to predict actual vigilance performance (% hits) for each subject in both the anodal and sham conditions. The “predicted” column describes %hits predicted using the CBFVL model while the “actual” column is the real %hits performance data from the study. %Errors are then shown next to the “predicted” column for the anodal and sham condition. The reader should note that these %errors differ from the ones mentioned earlier as these are for predicted performance (instead of %hits/baseline ratios; VP*).
Table 12. Applying the CBFV\textsubscript{l} model across subjects (Anodal vs. Sham)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time (mins)</th>
<th>% Hits (Anodal)</th>
<th>% Hits (Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted</td>
<td>Actual</td>
<td>%Error</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>88.10%</td>
<td>88.10%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>92.26%</td>
<td>90.00%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>87.26%</td>
<td>87.50%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>78.48%</td>
<td>94.74%</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>95.24%</td>
<td>95.24%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>95.27%</td>
<td>97.56%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>96.55%</td>
<td>97.44%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>105.87%</td>
<td>97.37%</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
<td>85.71%</td>
<td>85.71%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>78.64%</td>
<td>92.68%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>73.15%</td>
<td>94.87%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>67.30%</td>
<td>94.74%</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>97.62%</td>
<td>97.62%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>94.37%</td>
<td>97.50%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>98.27%</td>
<td>92.50%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>87.76%</td>
<td>94.74%</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>69.05%</td>
<td>69.05%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>68.19%</td>
<td>78.05%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>51.97%</td>
<td>64.10%</td>
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<td></td>
<td>40</td>
<td>55.17%</td>
<td>60.53%</td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td>97.62%</td>
<td>97.62%</td>
</tr>
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<td></td>
<td>20</td>
<td>133.87%</td>
<td>100.00%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>115.68%</td>
<td>94.87%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>107.61%</td>
<td>94.74%</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>95.24%</td>
<td>95.24%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>98.68%</td>
<td>95.00%</td>
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<td>30</td>
<td>97.65%</td>
<td>95.00%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>112.63%</td>
<td>100.00%</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>92.86%</td>
<td>92.86%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>93.06%</td>
<td>97.56%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>87.48%</td>
<td>97.44%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>85.85%</td>
<td>94.74%</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>76.19%</td>
<td>76.19%</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>84.21%</td>
<td>80.00%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>86.86%</td>
<td>60.00%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>90.32%</td>
<td>57.89%</td>
</tr>
</tbody>
</table>
Table 13 is an average of the %errors shown in table 12 above for the last 30 minutes. An overall average is provided at the bottom of the table.

Table 13. Average %error for the last 30 minutes across subjects

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Average %Error</th>
<th>Anodal</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.00% ± 0.00</td>
<td>0.00% ± 0.00</td>
<td>0.00% ± 0.00</td>
</tr>
<tr>
<td>20</td>
<td>8.65% ± 0.10</td>
<td>12.91% ± 0.11</td>
<td>12.91% ± 0.11</td>
</tr>
<tr>
<td>30</td>
<td>11.23% ± 0.10</td>
<td>16.62% ± 0.19</td>
<td>16.62% ± 0.19</td>
</tr>
<tr>
<td>40</td>
<td>14.60% ± 0.10</td>
<td>20.74% ± 0.20</td>
<td>20.74% ± 0.20</td>
</tr>
<tr>
<td>Average</td>
<td>11.49% ± 0.10</td>
<td>16.76% ± 0.17</td>
<td>16.76% ± 0.17</td>
</tr>
</tbody>
</table>

11.5 Heart Rate Model Analysis

Table 14 compares a model with CBFV$_L$ and the (HR-1)$^2$ terms with models that use only one of these terms. The CBFV$_L$, (HR-1)$^2$ model was not considered as a model (see table 10) because it has a high VIF (indicates high multi-collinearity between terms), while the other two models were considered.

Table 14. CBFV$_L$ and HR models

<table>
<thead>
<tr>
<th>Model Terms</th>
<th>$R^2_{\text{adjusted}}$</th>
<th>VIF</th>
<th>%Hits/Baseline=</th>
<th>%Error$_{\text{Avg}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBFV$_L$</td>
<td>0.957</td>
<td>N/A</td>
<td>3.9(CBFV$_L$)-2.9</td>
<td>13.36 ± 0.09</td>
</tr>
<tr>
<td>(HR-1)$^2$</td>
<td>0.967</td>
<td>N/A</td>
<td>202.5(HR-1)$^2$+1.0</td>
<td>25.27 ± 0.19</td>
</tr>
<tr>
<td>CBFV$_L$, (HR-1)$^2$</td>
<td>&lt;1</td>
<td>10.192</td>
<td>110.4(HR-1)$^2$+ 1.9(CBFV$L$)-1.0</td>
<td>16.17 ± 0.09</td>
</tr>
</tbody>
</table>

Figure 46 provides the HR* values during the anodal stimulation condition over time. Figure 47 plots average VP* ratios versus these HR* values to illustrate their quadratic relationship.
Figure 46. Shows the HR/Baseline ratio values over time during the anodal stimulation condition of vigilance task.

Figure 47. Illustrates the quadratic relationship that exists between vigilance performance and HR by plotting %hits/baseline against HR/baseline ratio values.
12.0 DISCUSSION

As the reader may recall, the aim of this thesis was to develop a model that predicted vigilance performance in both the real and sham condition using the physiological metrics collected from the McKinley Study (see chapter 9). Such a model would not only provide valuable insights about brain stimulation and its effect on vigilance performance but serve as starting framework for a general predictive vigilance model. Finally, if such a model could successfully approximate individual performance in both conditions it could provide as input signal to drive when to and for how long to apply tDCS.

12.1 Anodal Stimulation Performance Results

ANOVA analysis revealed that the mean performance in the anodal stimulation condition was statistically greater (p = 0.0004) than that found in the sham condition. Since sham stimulation provided 1mA stimulation for 30 seconds (compared to 10 minute 1mA stimulation in the real condition), it was assumed that the physiological effects of sham stimulation relative to anodal stimulation was negligible. The psychological effects, however, were assumed to be the same since sham stimulation provides skin sensations comparable to the real stimulation condition and these sensations often go away with time. Thus, it is likely that tDCS exerted a physiologic effect the resulted in increased vigilance performance relative to the sham stimulation condition. In this case increased neural activity in the dlPFC, as a result of tDCS, might result in increased top-down control over bottom-up processors (see background section) enabling subjects to better identify targets as they appear. Additional research is necessary to increase the understanding of these mechanisms.
12.2 Regression Analysis

12.2.1 Hypotheses Tests

As discussed in the methods section, it was hypothesized that CBFV_L^*, a CBFV_L^* x CBFV_R^* interaction term, and an A term (stimulation current amplitude) would be included in the final model. Conversely, it was thought that CBFV_R^*, rSO_{2,R}^*, rSO_{2,L}^*, HR^*, and age would not be included in the final model. As depicted in table 9, a majority of the hypothesized metrics had high R^2_{adjusted} values and statistical significance and combinations of these were considered for further testing to determine the “optimal model” (Table 10).

12.2.1.1 CBFV_L

As was expected, CBFV_L showed a good matching to vigilance performance while CBFV_R^* did not in the anodal stimulation condition. These hypotheses were largely driven by results from the Funke (2009) study who found the similar results in subjects not receiving stimulation. Since we know that anodal stimulation performance effects are largely physiological (section 12.1), the high R^2_{adjusted} value interestingly suggests that a large majority of the physiological-performance effects are accounted for or represented by CBFV_L^*.

It has long been thought that increased blood flow to the brain has served to provide essential cognitive resources, such as glucose and oxygen, in response to increased neural activity (Roy & Sherrington, 1890). The thought was that increased neural activity resulted in the release of vasoactive agents that result in the relaxation of vascular smooth muscles and corresponding increased blood flow (Roy and Sherrington, 1890 as cited in
Drake & Iadecola, 2007, p. 3)—termed functional hyperemia. Research years after have supported this relationship (though more complicated; see Drake & Iadecola, 2007)—showing that neurons and blood vessels are anatomically and functionally coupled (Drake & Iadecola, 2007) and that functional hyperemia and neural activity are temporally locked (Moore & Cao, 2008). More & Cao, (2008), however, hypothesize alternatively (and provide evidence) that increased blood flow serves to directly regulate neural processing (rather than in response to neural metabolic needs). Figure 48 depicts how both of these views might play out in the context of this study’s anodal stimulation condition results.

**Figure 48. Functional hyperemia by anodal stimulation.**

As discussed in the “A Potential New Intervention—Transcranial Direct Current Stimulation” section, we know that anodal stimulation generally results in increased neural activity—whether this is by neuromodulation in the short term or by increased synaptic strength by potentiation-like effects (e.g. LTP). By the traditional view of functional hyperemia, anodal stimulation would result in the increased probability of action potential firing (“P(AP)”) in the targeted brain region associated with vigilance performance decline (in this case the left hemisphere; see Funke, 2009). This increased neural activity results in the release of vasoactive agents that result in the corresponding change in CBFV. If we take the view provided by Moore and Cao (2008), anodal
stimulation activates a series of brain elements (e.g. astrocytes) that increases CBFV that in turn improves vigilance performance. The high $R^2_{\text{adjusted}}$ for this study supports either perspective and it is possible that some combination of both is taking place during the task.

12.2.1.2 $\text{CBFV}_R$

As expected, $\text{CBFV}_R^*$ did not have a high $R^2_{\text{adjusted}}$ value and was not included in the final model. This is not to say that the right hemisphere is not involved in vigilance, but rather does not show correspondence to the vigilance decrement in this particular task. Funke (2009), found that the overall mean CBFV in the right hemisphere was greater than that in the left, which supports previous findings that vigilance as lateralized to the right hemisphere (see “General Vigilance Systems” section). Funke, however, points out the fact that the vigilance decrement (instead of vigilance as a whole) was lateralized to the left hemisphere in this task and that other researchers have found similar results which suggests that vigilance performance more likely involves a complex interaction between both hemispheres. The fact that anodal stimulation to the right hemisphere also improved vigilance performance supports this idea (from McKinley Study; chapter 9).

12.2.1.3 $\text{CBFV}_L \times \text{CBFV}_R$

Surprisingly, no interaction existed between the left and right hemispheric blood flow velocities. Mathematically speaking, this is because $\text{CBFV}_R^*$ did not change much over the course of the task— which itself is not surprising. In Funke 2009, $\text{CBFV}_R^*$ also stayed relatively constant while $\text{CBFV}_L^*$ declined over time. It was thought, however, since Helton et al., (2010) found a de-lateralization in rSO$_2$ as vigilance task difficulty increased that $\text{CBFV}_R$ would interact with $\text{CBFV}_L^*$ as the subject became cognitively
fatigued. This relationship may certainly still exist and simply not be reflected in blood flow velocity changes.

12.2.1.4 \( rSO_2_{L} \) \& \( rSO_2_{R} \)

\( rSO_2^* \) did not show high \( R^2_{\text{adjusted}} \) values in either hemisphere as expected. One reason may be because of the positioning of the oximeter relative to the tDCS electrodes. Merzagora, et al., (2010) did show that dIPFC anodal tDCS led to increased oxygen saturation but did so using functional near-infrared spectroscopy directly under the site of stimulation. The oximeters were placed on the forehead and therefore only represent oxygen changes in the most rostral (frontal) portions of the cerebral cortex. tDCS electrode placement, in contrast, was more caudal (further back) and lateral (to the sides) relative to the oximeters. An MRI-derived finite element human head model in Datta et al., (2010) suggests that the distance between the electrodes and the oximeter pads does not matter because of the demonstrated lack of focality using traditional electrodes, as was the case in this study. Nitsche et al., (2007), however, demonstrate that anodal stimulation focality is increased when the cathode and anode size are increased and decreased respectively—which was the experimental approach in this study.

In another view, anodal stimulation might impact oxygen saturation levels relative to baseline but these changes in oxygen saturation simply may not couple with performance. Funke (2009) demonstrated that oxygen saturation does not correlate with CBFV*, which as discussed earlier is closely temporally-locked to neural activity in the brain. Further, it is well known that measured blood oxygenation levels far exceed the needs of brain tissue—not demonstrated by Fox and Raichle (1986) (as cited in Moore & Cao, 2007, p.
Therefore, for the purposes of this study, rSO$_2^*$ is not a good measure for vigilance performance.

12.2.1.5 **HR, Anodal Stimulation**

What was most surprising was the high relationship between the squared $HR^*$ term and vigilance performance under anodal stimulation. To further investigate this relationship additional analysis was performed that is discussed at the end of this section. Anodal stimulation, as expected, did show a strong relationship with vigilance performance. As a performance metric it is not useful, however, since in the real-world, periods of time will exist where individuals are not being stimulated.

12.2.2 **Optimal Model Selection**

After applying the selection methodologies described in the methods section, 10 models remained for consideration (see table 10). Of these 10 models, the linear $CBFV_{L^*}$ was selected as the optimal model for the purposes of this thesis. An interesting point to make here is that the more complicated models (e.g. non-linear, more than one term) could not outperform the very simple blood flow model. This suggests that vigilance performance is particularly sensitive and directly related to blood flow changes in the brain. Table 11 shows that the model meets all the assumptions of linear regression which says that the model can be used to predict performance.

12.3 **The Left Cerebral Blood Flow Velocity Model: Anodal vs. Sham Conditions**

Of course, the cerebral blood flow velocity model is more useful (especially when driving a stimulator) when it applies to both anodal and sham conditions. If so, it suggests that the relationship that $CBFV_{L^*}$ has with vigilance performance (at least for
this task) remains unchanged regardless of the experimental condition. From a scientific standpoint this says that the effects of 10 minute anodal brain stimulation—whatever those effects are, can be accounted for by CBFV_L^*. From an application standpoint it says that the model is ideal for driving a stimulator (i.e. when and how long to stimulate) because it provides a continuous approximation of vigilance performance during both stimulation conditions.

Figure 42 provides three plots that illustrate the coupling of the CBFV_L^* ratios and vigilance performance. Looking at figure 42b, whose y-axis is scaled the same as the axis in plot 1 and illustrates the performance ratios for both conditions, it appears that no relationship exists between the CBFV_L^* in either condition. In fact, relative to VP^* changes CBFV_L^* does not change much at all over time. Figure 42c, however, whose y-axis range is significantly smaller, shows that CBFV_L^* is highly related to the VP^* for both conditions. This findings show that vigilance performance is extraordinarily sensitive to small changes in CBFV^* in the left hemisphere.

To see a quantitative representation of the relationship CBFV_L^* has with vigilance performance, a best fit line relating VP^* to CBFV_L^* in both conditions Figure 43 was created. The equations, which are provided below, are identical to one significant figure—showing that the relationship between CBFV_L^* remains unchanged during real stimulation.

\[
\begin{align*}
\text{VP}_{\text{anodal}}^* &= 3.8849(CBFV_L^*) - 2.8901 \quad \text{(Equation 15)} \\
\text{VP}_{\text{sham}}^* &= 3.9165(CBFV_L^*) - 2.9003 \quad \text{(Equation 16)}
\end{align*}
\]
Figure 44 illustrates that the CBFV_L model can successfully be used to indicate performance in both conditions of actual averaged performance (average %hits) while figure 45 shows the same thing quantitatively with “actual vs. predicted” slopes of 0.86 and 0.93 for the anodal and sham conditions respectively. The reader should, however, exercise caution when interpreting these results as they all depend on averages of the entire subject pool. Applying the model for each subject in the anodal and sham conditions shows that the model works far better for some subjects than others and is far from perfect overall (Table 12; Table 13). This biased coupling may represent individual differences between subjects and their physiological response to vigilance tasks. Less than perfect fit also suggests that other mechanisms may exist that are not accounted for by blood flow velocity changes. For example, some subjects might rely on stored energy in the form of glycogen (see Carlson, 2010) instead of that provided by cerebral blood flow. In this case, blood flow would not change but performance would because of the increased capacity for neuronal cell metabolism. Further experimentation is required to tease out these potential other effects that are not accounted for by changes in CBFV.

Also, the model does not fit as well as time progresses and predicted performance tends to undershoot actual performance—especially in the sham stimulation condition (Table 12; Table 13). It is possible, in this case that the relationship between CBFV_L and vigilance performance is changing over time and/or that other physiological changes are taking place that are not accounted for by CBFV_L with time (i.e. another essential input variable might exist that was not investigated). Further investigation is necessary to parse out these effects.
12.4 Predicting Performance Using the Left Cerebral Blood Flow Velocity Model & Heart Rate Model Analysis

Table 14 summarizes regression analysis results that shed light on some of the quadratic HR term mentioned in section 11.2.1.5 above. The first two rows shows the CBFV\textsubscript{L} and (HR-1\textsuperscript{2}) models that were considered for final model selection (see table 14). As discussed earlier, the CBFV\textsubscript{L} model was selected as the best model because of its relatively low $\%\text{error}_{\text{Avg}}$ (13.36 ± 0.09 compared to 25.27 ± 0.19 for the heart rate model). The (HR-1\textsuperscript{2}) model, however does have a high $R^2_{\text{adjusted}}$ (higher than the CBFV\textsubscript{L} model in fact) for the averaged performance ratio data set, which suggests that heart rate changes may represent some of the physiological changes occurring during the vigilance task. Although HR itself does not always match vigilance performance (see background section)—which was the case in this study, the (HR-1\textsuperscript{2}) term might be a partial representation of heart rate variability which has shown relationships to vigilance performance (Eisenberg & Richman, 2011). If “1”, which is the represents the baseline performance value is treated as the mean $\mu$ the reader will notice (HR-1\textsuperscript{2}) term in the equation is similar in structure to the equation for variance.

$$VP^* = 202.5(HR - 1)^2 + 1.0$$ \hspace{1cm} \text{Equation 17}

$$Var(X) = E[(X - \mu)^2]$$ \hspace{1cm} \text{Equation 18}

Changes in heart rate depicted in figure 46 and figure 47 suggest that dlPFC anodal stimulation decreased heart rate as $HR^*$ decreased during stimulation (10-20 minutes) and began returning to baseline immediately after stimulation (20-40 minutes). Recently, Green et al., (2010) were able to alter systolic and diastolic blood pressure and heart rate using deep brain stimulation of the periaqueductal grey matter in the midbrain. The authors concluded that these changes were caused by modulating the autonomic system.
Though the dIPFC is anatomically distant from PAG, studies have shown that the prefrontal cortex also has direct relationships with the autonomic nervous system (ANS) (Sakatani, Tanida, & Katsuyama, 2010; Barbas, Saha, Rempel-Clower, & Ghasshghaei, 2003). Even more recently, Montenegro et al., (2011) significantly increased HR variability in athletes by stimulating their temporal lobes using anodal tDCS. Therefore, heart rate changes in this task may simply reflect a secondary side effect, beyond CBFV changes, by modulating the ANS.
13.0 CONTRIBUTIONS AND APPLICATIONS OF RESEARCH

The CBFV_L model provides several potential applications and contributions in both the real-world and research settings. These include:

1. a physiological performance metric than can be used to drive a tDCS device
2. insight on the physiological effects caused by tDCS
3. evidence that an individual’s performance can be described and modeled relative to their baseline rather than as an absolute value
4. a tool to design/study:
   a. optimized tDCS protocols (e.g. stimulation time and intensity)
   b. the effects of real-world tasks on vigilance performance
   c. user-interfaces and work environments where task success depends on vigilance performance
5. a starting foundation for a model capable of predicting the effects of tDCS on vigilance performance

Though not perfect, the CBFV_L model provides a continuous sense of an individual’s vigilance state relative to their baseline. As mentioned at the beginning of this thesis, this information can be used to drive a stimulator in a negative feedback system. In this case, CBFV_L would serve as the input into the feedback loop. The system would then use the CBFV_L model to determine an approximation of vigilance performance which would be used to indicate whether stimulation is needed or not. From a research perspective the results from this study show that a large majority of the physiological effects caused by tDCS can be accounted for by CBFV. This is useful because it suggests blood flow as a candidate endpoint or intervening point in a conceptual model (e.g. Figure 48) relating
and describing the mechanisms of brain stimulation and its effect on cognition. Additionally, the study showed that the relationship CBFV_L has with vigilance performance during the 40 minute task does not change under stimulation. From a research perspective this suggests that tDCS exerts its physiologic effects not by changing vigilance-CBFV_L relationships but by changing factors that influence CBFV_L—again making it an ideal candidate for driving a stimulation device. Since the majority of vigilance researchers are interested in studying absolute vigilance performance changes (e.g. %hits, number of false alarms) they are often limited to describing and applying their results in a general sense. Vigilance performance, however, varies from individual-to-individual and on a day-to-day basis. By normalizing, describing and modeling vigilance performance relative to individual baseline, however, vigilance changes can be attributed on an individual basis. This thesis provides support for this approach by predicting vigilance performance (with some %error) on an individual basis by using a model that predicts vigilance performance relative to individual baseline.

From a more practical standpoint the CBFV_L model provides a sense of vigilance performance in scenarios when no formalized measure is available (unlike in the research laboratory). With such an ability, the model can be used as a tool to optimize tDCS stimulation protocols in real-world environments—particularly those whose success depend heavily on vigilance performance. From another perspective the model can be used to gain a sense of vigilance performance during tasks where CBFV_L is measured. To take this idea a step further, user-interfaces and work environments can be modified or tested in ways that improve vigilance performance during these tasks (or vigilance overall) as indicated by the CBFV_L model. Finally, as discussed in the rationale section
of this thesis, this model can serve as starting foundation point for developing a model capable of predicting the effects of brain stimulation on vigilance performance.
14.0 FUTURE RESEARCH CONSIDERATIONS

Given the limitations of the study used to develop the CBFV₁ model several future research considerations exist. These include:

1. Validation of the model against an independent data set

2. Application with/for/in:
   a. smaller time windows
   b. longer time periods
   c. real-world settings

3. Investigate:
   a. other metrics not used in the McKinley Study
   b. why the model works better for some and not others (i.e. individual differences)

4. Model improvements:
   a. pair with other models or metrics—especially those that are more fieldable
   b. metrics that approximate a subject’s baseline state

Good and Hardin, (2003), stress the importance of model validation because not doing so can result in invalid conclusions. In one view, the CBFV₁ relationship was validated by independently verifying it with two separate data sets— the anodal and sham conditions, which were collected on separate days during different time periods. Model validity, would be more convincing, however, if it was validated with an entirely new pool of subjects. Additionally, a larger sample size would be preferable. Since subject variability is high in vigilance tasks, the current small sample size may not adequately
represent the target human population. Future tDCS studies should be designed with these considerations in mind.

Vigilance researchers often break vigilance tasks into 10 minute time periods (Warm, Matthews, Parasuraman, 2009; Hitchcock et al., 2003) though smaller time periods have been used (Helton et al., 2007; Mayleben et al., 1998). This is likely because 10 minute periods do a satisfactory job removing subject performance variability that occurs over time during a vigilance task—the rationale for this study’s approach. The model’s ability to be tested during time periods less than 10 minutes should be considered, however. In general, appropriate time periods of course depend on the task or scenario the model is being applied to (e.g. changes over 5 minutes may be more important in tasks where vigilance decrements occur rapidly). A model that can be applied with smaller time periods will, however, have a higher temporal resolution. Further, though it is clear that blood flow and changes in neural activation are linked, these changes may not be immediate and therefore not reflected in the CBFV_L model applied with smaller time periods. Therefore, applying the model during shorter time periods should be considered.

An additional limitation is that the model can only be applied for a 40 minute task, 20 minutes after 10 minute stimulation. Ideally, the model should function in varying scenarios for periods of time beyond 40 minutes. Studies that at least allow for the effects of stimulation to “wear-off” (i.e. performance to return to sham stimulation levels) should be considered. If tDCS is applied in the real-world setting it is likely that it will be used more than once during a task. Therefore, studies that have more than one period of stimulation and no stimulation should also be considered. It should also be acknowledged, that the laboratory and real-world environments are not at all equivalent.
Real-world tasks that require vigilance may be substantially more stressful (e.g. air traffic controller task), cognitively demanding, less-controlled (e.g. temperature and environment) and usually requires several cognitive skill sets in addition to vigilance. Therefore, it is important that these modeling approaches be investigated in tasks or fashions that are more comparable to the real-world environment and at some time investigated in the actual real-world environment.

The metrics used in the McKinley Study, which were used to develop the model for this thesis, are only but few metrics that could be examined for model development. Though, no one has attempted to develop a vigilance model in the context of brain stimulation (to the author’s knowledge), several attempts have been made over the years in developing vigilance monitoring systems—particularly for monitoring driver vigilance. Examples include head and facial tracking systems (e.g. blink frequency, head motion analysis) (Bergasa, Nuevo, Sotelo, Barea, & Lopez, 2006; Ji and Yang, 2002) and by other physiological metrics such respiration, electrocardiogram, electromyogram, and skin conductance (Healey and Picard, 2000 as cited in Bergasa et al., Nuevo, 2006, p.63). Technologies such as these should be considered as alternate metrics or metrics that can be used in parallel with CBFV\textsubscript{L} model.

Additionally, using more than one model in parallel rather than together in one model might yield better results than one model alone. CBFV\textsubscript{L} that increases while HR\textsuperscript{2} decreases might represent something different than when HR\textsuperscript{2} is increasing. A variation of the McKinley, (2009) acceleration stress model, which can calculate neural metabolism and corresponding cognitive performance using rSO\textsubscript{2}, might also be considered in future vigilance model development studies. Models and/or metrics that
can indicate or predict subject baseline state might also be considered; since operators may not always have time to determine baseline performance during real-world tasks.
15.0 CONCLUSIONS

This thesis set out to answer three questions that are restated here:

1) How well can the averaged normalized vigilance performance (VP*avg) — both during and after tDCS, be predicted using the average (across subjects) of any if not all of the following metrics: right and left hemispheric cerebral blood flow velocity (CBFV), regional cerebral oxygen saturation (rSO2), heart rate (HR) and the stimulation parameters (e.g. location and polarity) used in the McKinley Study (see chapter 9)?

2) Which of these metrics (or input variables) are key in predicting VP*avg. (during and after tDCS) and hence tDCS-vigilance effects for both real and control (anodal and sham respectively) stimulation conditions?

3) How well can VP*avg. be used to predict vigilance performance (% hits) in individual subjects—both during and after tDCS for both real and control stimulation conditions?

CBFVL and a (HR-1)^2 term accounted for about 95.7% and 96.7% of the variance present in the data set. Extensive analysis of the CBFVL model suggests that CBFVL generally performs well in indicating (i.e. predicting) individual vigilance performance, both during and after tDCS for both real and control stimulation conditions. The model, however, is ideal for some subjects and not so for others. Additionally, the model is limited to the 40 minute vigilance task in the McKinley Study. If the model is to be improved, subject individual differences must be identified and longer vigilance tests with varying stimulation protocols carried out. As whole, the model is an important first
step towards creating accurate vigilance metrics that can be used to drive stimulators as well as predict performance while using these technologies in the real-world environment.
16.0 WORKS CITED


George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology Reviews, 35*, 301-316.


