ABSTRACT

Title of Document: PERFORMANCE UNDER PRESSURE: EXAMINATION OF RELEVANT NEUROBIOLOGICAL AND GENETIC INFLUENCE

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Satisfactory human performance demands the complex interaction of multiple factors such as arousal/motivation, emotion expression and regulation, intricate synchronization of central and peripheral motor processes, all recruited in the service of adaptive, moment to moment decision making. The segregation of these various factors aids in the understanding of their complex interactions. Recently, scientific investigation has focused on understanding the integration of these various factors. The complementary role of emotion and cognition in successful human performance is emphasized. As a viable metric of emotion regulation differences in asymmetry of human brain frontal activity have traditionally been utilized to index certain trait predispositions within the approach/withdrawal dimension of emotion/motivation. Researchers have begun to make a case for an acute or state difference in frontal asymmetry. This “Capability Model” posits the neural underpinnings of the relative

difference in electrical activity between the left and right frontal lobes as a phasic/situational mechanism possibly sub-serving the integration of emotion and cognition during challenge. The current study demonstrates support for this situational/state model of frontal asymmetry. Thirty channels of EEG were collected along with, skin conductance, heart rate and acoustic startle amplitudes while subjects were engaged in two levels of a working memory task under three increasing levels of stress (final level=electric stimuli/shock). Hierarchical regression results implicate state frontal asymmetry differences as having a mediating role in the adaptive regulation of emotion during enhanced performance on an N-back working memory task but only in the high stress condition. During shock /threat of shock participants with higher state asymmetry scores showed significant attenuation of eye-blink startle magnitudes, faster reaction times and increased accuracy. This suggests an integration of emotion and cognition.

PERFORMANCE UNDER PRESSURE: EXAMINATION OF RELEVANT NEUROBIOLOGICAL AND GENETIC INFLUENCE

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Chapter I: Introduction

This study is explicitly interested in the integration of emotion and cognition during "performance under pressure." Satisfactory human performance has been extensively studied within the context of skilled motor behavior (Hatfield et al., 2004). The integration of emotion, cognition and purposeful movement in congruence with adaptive goals is at once one of the more complex and demanding challenges of human social interactions and difficult to examine in laboratory settings . Results derived from athletic performance may be legitimately translated into domains known to elicit the highest levels of stress, such as 1st responders, emergency/surgical medicine and police, military and rescue operations. The benefits of understanding aspects of the central nervous systems (CNS) role in successful navigation within the highly visible domains outlined above are readily apparent. However, much can be gained from this same insight with regards to other realms of day to day cognitive/cognitive-motor performance such as athletic, job and academic achievement, parenting, public speaking, safe driving and on and on.

Emotion Regulation and Frontal Lobe Influence

In this regard the frontal lobes are instrumental in the regulation of emotion. More specifically the left frontal region has been clearly shown to manage arousal and regulate the stress response (return to homeostasis), while the right frontal region sympathetically orchestrates the fight or flight response (Criag, 2005). A reliable correlate of this left frontal executive influence is found in the Frontal symmetry difference score (Fads) (Allen & Kline, 2004; Coan & Allen, 2004;

Davidson, 2004). The Fads represents the relative difference in frontal activation between homologous measures of EEG alpha power assessed at right and left frontal sites (F4-F3). The neuroanatomical circuitry of emotion regulation is briefly outlined as such. For automatic regulation, the amygdala is widely agreed upon to initiate the arousal associated with fear/anxiety and its putative control centers (i.e., the brakes) appear to be in ventromedial Prefrontal Cortex (vmPFC/sACC) subgenual Anterior Cingulate Cortex and for deliberate regulation, the amygdala (of central hub status) (Pessoa, 2008; Sporns et al., 2007; Young et al., 1994) derives the affective salience (Ghashghaei et al., 2007) of sensory stimuli, amplifies relevant aspects of such stimuli through initiation of autonomic nervous systems (ANS) arousal mechanisms and deliver this enhanced (Anderson & Phelps, 2002; Egner & Hirsch, 2005; Glascher et al., 2007; Sharot & Phelps, 2004) package to the ACC/vmPFC (reciprocally connected to amygdala). From here the information stream enters multi-sensory receiving/integrative and reward evaluation zones in the OrbitoFrontal Cortex OFC (Davidson, 2004; Kringlebach & Rolls, 2004; Pizzagalli et al., 2005; Rolls, 2004; 2005). The dorso- and ventro-Lateral Prefrontal Cortex (D- & V-LPFC) to which the OFC is bi-directionally connected, then incorporates these privileged (Davidson et al., 2004; Ishai et al., 2004) messages in order to adaptively exert executive control over goal-oriented behavior (Damasio, 1994; Ghashghaei et al., 2007; Gray et al., 2002; Gray, 2004; Ochsner & Gross, 2005; Rolls, 2005; Wilenski, 2006). LPFC executive influence in this framework would be seen as both local activity and feedback through the aforementioned circuits with the goal(s) (among others) of up- or down- regulating amygdala activity. Relevant fMRI results by

Ochsner et al.,(2002), implicate left frontal activity in the regulation of arousal as indexed by inverse activation profiles of left DLPFC with the amygdala. Further support for the differential role of left and right frontal regions was noted by Craig, (2005), who reported robust activation in the left anterior Insula during relative parasympathetic expression and strong relative activation in the right anterior Insula during sympathetic expression. Multiple PFC regions and the networks in which they are embedded are intimately involved with the integration of emotion, cognition and motivation and are known to be functionally connected (Damasio, 1994; Davidson, 2004; Ghashghaei et al., 2007; Kringelbach & Rolls, 2004; Ochsner et al., 2002; Pizzagalli et al., 2005; Quirk & Beer, 2006; Rolls, 2004; 2005; Vogt, 2005) to the sustained firing (Adcock et al., 2000; Dolcos et al., 2008; Fuster, 1997; Rolls, 2004; Sakai, 2002) necessary for the maintenance of short-term memory trace found in the DLPFC, the putative source of the signal that gives rise to the EEG-derived Fads (Pizzagalli et al., 2005).

Traditionally emotion has been thought of as having a negative influence upon cognition, "if you want to see this clearly you must take your feelings out of it," is an often echoed bit of advice. In stark contrast to those words a large body of work from Damasio and colleagues (Bechara et al., 1997; Bechara, 2000; Damasio, 1994; 1996) has shown that rational thought (cognition) functions at significantly more adaptive levels when integrated with emotion. The 'Iowa Gambling Task' assesses the ability of subjects to choose a long over short term benefit, patients with lesions in affective regions of the brain perform significantly below the level of controls. Historically, a behavioral perspective has dominated studies of emotion regulation. However, its

exploration via the biobehavioral approach of affective neuroscience has added both depth and breadth. The resultant corpus of work has revealed much about the neural underpinnings of emotion regulation (Davis & Myers, 2007; Phelps & LeDoux, 2005; Quirk & Beer, 2006;.Quirk & Mueller, 2008; Sotres-Bayon et al., 2004; 2006; Wilenski et al., 2006). Through examination of both its unconscious (automatic) and conscious (deliberate) mechanisms, two major sources have come to dominate the work in emotion regulation

First, work from animal research has investigated fear, using classical conditioning paradigms (LeDoux, 2003; Maren & Quirk, 2004; Quirk et al., 2003; Quirk & Beer, 2006; Quirk & Mueller, 2008; Pare et al., 2004; Rodrigues et al., 2004) by pairing auditory stimuli with foot-shock. Aspects of emotion regulation are then examined by manipulating various temporal, behavioral and molecular elements of extinction (the most fundamental form of emotion regulation). Second, work from human imaging research (Anders et al., 2004; Blair et al., 2006; 2007; Critchley et al., 2002; Dolcos et al., 2004; 2008; Dolcos & McCarthy, 2006; Egner et al., 2007; Gray et al., 2002; Kalisch et al., 2006; Lee et al., 2008; Luo et al., 2007; Ochsner et al., 2002; 2004; Phelps et al., 2004; Schaferet al., 2002) follows one of two basic paradigmatic paths. In the first model participants actively suppress or enhance emotional experience (expression) elicited from memory and or affectively laden stimuli such as film clips or photos. While in the second model participants are presented similar affective probes along with more potent stimuli such as shock /threat of shock and are asked to regulate emotional influence/interference during challenging working memory (WM) tasks.

Individual Differences & Frontal Asymmetry

The construct of individual differences has been successfully employed to gain better resolution of the brain processes derived from the complex hierarchical networks briefly sketched above. Davidson & Irwin, (1995), have coined the term 'affective style' to describe one's predisposition to act a certain way during a range of emotional challenges. An example might be: predicting the wide range of individual response to the challenge of public speaking via an agreed upon index of predisposition. Historically, the science of individual differences has grouped people based upon psychological evaluation techniques such as self–report on valid and reliable questionnaires and or their performance on standardized, ambiguous tasks (Coan et al., 2006; Endler, 1997; Mischel et al., 2002). Currently, cognitive-neuroscience assesses theory-driven combinations of biological markers (genes, molecular processes & psychophysiologic response, including BOLD) during various cognitive-emotional challenge (along with self-report) in order to better understand individual differences at multiple levels of analysis and across varied situations. An important example of this is found in the Etkin et al, (2004), human imaging (fMRI) study in which unconscious activation of the basolateral amygdala to fearful stimuli was found only when individual differences in trait anxiety were considered as a grouping variable.

As a viable metric of the approach-withdrawal dimension of emotion regulation and subsequently a marker of individual difference, the EEG-derived Fads has established considerable support. Individuals with higher positive vs. negative Fads fare better at the management (resilience) of negative emotional stimuli. The

bulk of this research has been conducted with resting or Trait Fads as a predictor of outcomes on both self-report and bio-chemical measures, while studies that have examined correlates of the phasic metric induce acute affect changes and then measure the resultant state Fads (Allen & Kline, 2004; Coan & Allen, 2003; 2004; Davidson, 2004). A causal link between Fads and emotional valence was established by Allen et al., (2001), who employed EEG neuro-feedback training over five separate sessions. Subjects were able to either increase or decrease their trait Fads (depending on the training intent). Notably these changes were accompanied by significant differences (predicted) in pre- vs. post-training measures of facial EMG response to varied emotion-eliciting stimuli. Specifically elevations of Fads resulted in positive affect, while conversely depressions of Fads resulted in negative affect.

Trait measures of Phasic Phenomenon & the 'Capability Model'

One of the central problems in measuring emotion regulation via the assessments derived from trait measures such as self-report, genotype and resting Fads is that emotion regulation itself is a phasic/situational process. Thus, state measures of its neural correlates may explain more of the variability observed in relevant behavioral outcomes (Coan et al., 2006). Anecdotally, most of us have experienced conversations containing statements such as "she is a pretty good most of the time but a real clutch player in the post-season." This 'capabilities' view of disposition is supported both by the work of Mischel and colleagues (Mischel et al., 2002) and by the well-tested situational framework found in Endler's, 1997, "multi-dimensional interactional model." Endler's model has demonstrated the ability of person-situation-environment relations/integration to explain additional variability in

behavior, when contrasted with the more typical trait measures of personality described above. Coan et al., 2006, have proposed a 'capability model' for the individual differences described by the Fads, in which they state, "while the dispositional model of Fads aims to measure individual approach versus withdrawal disposition *regardless of situation*, the capability model aims to measure the degree to which individuals are capable of approach versus withdrawal responses, or, importantly, of inhibiting those responses *depending on the demands of the situation*" (Coan et al, 2006, p.198). In this important study they highlight previously inconsistent results obtained using resting measurements of emotion regulation via the Fads metric, such as: reference scheme error, lab setting & experimenter effects (Hagemann, 2004), situational changes in subjects daily routine (i.e., just failed an important exam) and negatively characterized affect associated with relative left frontal activation (Harmon-Jones, 2003). Remarkably Coan et al. 2006, found: 1-Individual differences in Fads are more marked during state vs. resting conditions, 2-individual differences during state vs. resting conditions are less susceptible to artifact introduced by the problems outlined above such as reference scheme and 3-state measures of Fads are more reliably correlated to self-reported measures of affective personality characteristics. Perhaps, the strongest finding in their study was, using a G-theory model and obtaining Fads across five different emotion inductions and at rest, that 50% of the variance in Fads was explained via an individual by condition interaction as compared to 26% with resting Fads alone.

In order to test the viability of the 'capability model,' it is essential to challenge study participants with increasing levels of psychological stress.

Accordingly, a thoughtful strategy for the achievement of increasing levels of stress is through a combination of emotion eliciting stimuli, such as the international affective picture system (IAPS, Lang et al., 1999) and the introduction of nociceptive stimulation such as transcutaneous electric nerve stimulation (TENS, Johnson et al., 1991). Convergent evidence for the emotion regulatory role indexed by Fads can be provided by concurrent assessment of the eyeblink startle response. Numerous studies have supported the efficacy of the eyeblink startle measure as a reliable indicator of emotion regulation (Blumenthal et al., 2005; Bradley et al., 1999; 2006; Greenwald et al., 1998). The majority of studies that have examined state frontal asymmetry have done so by noting the effects of phasic emotion induction on the Fads (Coan et al., 2006; Coan & Allen, 2003; Davidson et al., 2000; Gable & Harmon-Jones, 2008; Harmon-Jones et al., 2006; Hoffman et al., 2005). There are no studies we are aware of, to date, in which behavioral outcomes (performance-speed & accuracy) and situational measures of automatic/unconscious emotion regulation (difference in eyeblink startle amplitudes-see methods, p.19-20) are examined as dependent measures, as a function of trait and state Fads as predictor variables Using a hierarchical regression approach in which trait Fads is entered as the initial model, we predict that the addition of state Fads will significantly increase explained variance during higher levels of anxious arousal for all three dependent variables noted above.

In the present study participants will be challenged with working memory tasks representative of a fundamental dimension of cognition (verbal vs. spatial) under three progressive levels of psychological stress. The explained variance for "performance under pressure" provided by the state measures of Fads will be notably

increased under the highest levels of anxious arousal. In addition temporal and parietal state asymmetry measures during the highest levels of arousal will be assessed in order to investigate topographical specificity, no significant relationships are expected, thus indicating the unique role of the frontal lobes in emotion-cognition interactions

Overview

The overarching purpose of the program of research summarized herein is the examination of arousal and cognitive motor performance. Further, the attempt was to advance our understanding of the arousal-performance relationship beyond the behavioral perspective typically employed to study the influence of arousal on performance. Satisfactory performance demands appropriate levels of arousal/motivation. The inverted-U theory of arousal/performance claims that the specific demands of a task dictate the adaptive level of arousal. For example power lifting may warrant very high levels of arousal as it is a gross motor skill, whereas performing an intricate surgery calls for moderate levels of arousal. Regulating arousal/emotion is a critical skill in navigating the complexity of human social interactions.. This study assesses cortical dynamics, with particular focus on the role of frontal activation, as well as relevant genetic markers, to explain variance in cognitive performance under varying levels of stress. Importantly, the study attempted to significantly elevate the magnitude of psychological stress relative to previous work from our lab. The primary metric examined was that of asymmetry of frontal EEG alpha. Years of research examining the electroencephalographic (EEG)-derived frontal asymmetry difference score (Fads) suggests it may be a reliable index

of one's disposition to successfully regulate the approach-withdrawal dimension of emotion and, therefore, possibly moderate the arousal-performance relationship. Fads is a relative measure indexing the difference in alpha (8-13 Hz) power from homologous right and left frontal electrodes, the more positive the score, the more relative left frontal activation. It is this left frontal activation (relative to right) that has been associated with more of an approach-related orientation and enhanced emotion regulation. Negative Fads scores imply greater right frontal activation and a withdrawal from challenge likely due to a failure to manage negative affect. Specific regions in the human frontal lobe are known to mediate both executive cognition and emotion regulation processes and perhaps even more importantly their interactions. Evidence accrues for the notion that; the role of frontal asymmetry in emotion regulation may be better assessed by consideration of both trait and state measures of Fads. Such conjoint consideration may explain greater variability in performance than by assessment of resting Fads, alone. Additionally, for the purpose of this investigation the amplitude of the eyeblink startle response will serve as an operational definition of automatic emotion regulation that would be moderated by frontal asymmetry.

Beyond individual differences in emotion regulation, the influence of arousal on performance is also related to specific domains of task demands. For example, in the cognitive domain, working memory tasks involving visuo-spatial challenge suffer greater decrement during excessive arousal (threat of shock) than do verbal tasks. This phenomenon, supported in the extant literature, results from differential involvement of the right frontal lobe with the representation of negative affect,

thereby, increasing its susceptibility to resource depletion during right-lateralized challenges, such as visuo-spatial working memory. Such specificity of hemispheric engagement implies that the nature of the task (verbal vs. spatial vs. cognitive-motor) must be carefully considered to predict the impact of arousal on performance.

Therefore, it is hypothesized that those with positive-resting-Fads (associated with successful regulation of emotion (resilience) and more of an active-coping approach orientation toward the stressors of daily life) will perform better under stress than those with negative resting-Fads, and that this will be more pronounced during the visuo-spatial working memory task. Furthermore, consideration of state Fads is likely to explain additional variation in task performance and eyeblink startle magnitude. Finally, individual differences in affective disposition are likely influenced by genotypic variation. To clarify the contribution of genotype on emotion regulation, the influence of two-single nucleotide polymorphisms (SNPs located on COMT and 5 -HTT) on emotion regulatory processes will also be examined.

To address these issues a two-part study (Study 2) will be conducted. In part 1, individuals representative of two populations regarding dispositional affect (approach and withdrawal oriented) will be challenged with low, moderate and high arousal conditions while negotiating both left- and right-hemispheric tasks. As such, cognitive performance scores will be subjected to a 2 x 3 x 2 (Group x Stress induction x Task) ANOVA by which the interactive effects of resting Fads, arousal, and task type on performance and eyeblink startle magnitude will be examined. In part 2 a series of hierarchical regression analyses will be conducted to assess the relationship between cognitive performance & eyeblink startle magnitude and (1)

dispositional affect or resting Fads (2) genetic influence (3) phasic frontal emotion regulation or state Fads, as well as the gene-environment interactions of (4) gene x resting Fads and (5) gene x state Fads to explain additional and unique variation in cognitive performance under different levels of stress induction beyond that provided by assessment of resting Fads, alone. More specifically, 2 series of 6 separate regressions will be conducted for each of the two tasks within the three arousal conditions.

Statement of the Problem:

In order to examine the person-environment interaction and better explain the arousal-performance relationship a 2 (group) x 3 (level of arousal) x 2 (task type) ANOVA will be employed to determine interactive effects between Fads (person factor), arousal, and task type. Specifically, using the grouping variable (Fads disposition) as a marker of individual difference in emotion regulation and tracking the direction of its covariance with the different arousal x task interactions and both performance & eyeblink startle magnitude outcomes we intend to better elucidate the emotion-cognition relationship. The positive-Fads group will exhibit an inverted-U shape trajectory regarding performance between the three arousal conditions during the spatial task, while the negative-Fads subjects will show a much attenuated, inverted-U, which will more closely resemble a negative linear relationship between performance and arousal. The magnitude of difference in performance (positive resting Fads = better performance) between groups will increase as level of arousal increases. Performance on the verbal task will decrease between neutral and negative conditions and remain essentially the same between negative and nociceptive

conditions with the magnitude of difference between the positive and negative resting Fads groups much reduced. Eyeblink startle magnitudes will be inversely related to performance results.

Further, in a complementary, hierarchical regression, we predict that during the negative and nociceptive conditions, the magnitude of state-Fads will predict the magnitude of both performance (higher state fads = better performance) and eyeblink startle (higher state-Fads = lower eyeblink startle). Within the context of our experimental design a positive state-Fads may in fact look (it is hypothesized) analogous to Gray et al's integration of emotion and cognition. It is believed that the combination of theses two metrics (resting- & state-Fads) may provide a more reliable marker of emotion regulation to be utilized in future interventions.

Through the application of additional hierarchical regressions, the association of specific allelic variants of genes known to influence emotion regulation will be assessed for addition of significant explained variance,

Comment: The three levels of fear induction are designed to reveal the obligatory three marks on the arousal/performance curve described by the theoretical constraints of inverted-U. The shock, or threat of shock condition is primarily designed to induce excess arousal for purposes of disrupting performance. However, as Harmon-Jones et al, 2006, has shown that self-relevance increases the magnitude of state-Fads, we theorize that pain as the most basic of the self-relevant emotional/motivational processes will increase detection of directional changes in the state-Fads metric and provide cleaner inferences.

Hypotheses:

(#1 & 2, ANOVAs – (2 x 3 x 2) (Group x Stress induction x Task):

(**Hypothesis 1**) The positive-resting-Fads group will exhibit attenuated eye-blink startle relative to the negative resting-Fads group under stress. Furthermore, the magnitude of difference between the groups will be positively related to stress.

(**Hypothesis 2**) The positive-resting-Fads group will exhibit superior cognitive performance relative to the negative resting-Fads group under stress. Furthermore, the magnitude of difference between the groups will be positively related to stress and will be more pronounced during the visuo-spatial working memory challenge.

(#3-10, Hierarchical Regression Models)

Hypotheses 3-10: Cognitive performance (reaction times & accuracy) & eyeblink startle magnitude as dependent variables, with independent variables; (1) resting Fads (2) genetic influence (3) state Fads x condition (4) gene x resting Fads, and (5) gene x state Fads

State Frontal asymmetry predictions:

(Hypothesis 3) State Fads will account for additional and unique variance in emotion regulation as measured by the amplitude of eye-blink startle EMG beyond that provided by resting Fads. The magnitude of the influence of state Fads will be greater under increased levels of stress.

(Hypothesis 4) State Fads will account for additional and unique variance in cognitive performance beyond that provided by resting Fads. The magnitude of the influence of state Fads will be greater under increased levels of stress and for the visual-spatial challenge.

Genetic influence predictions:

(Hypothesis 5) Genotypic variation will account for additional variance of emotion regulation (eyeblink startle magnitude) above and beyond that explained by resting Fads.

(Hypothesis 6) Genotypic variation will account for additional variance in cognitive performance above and beyond that explained by resting Fads.

(Hypothesis 7) There will be a gene-environment interactive effect such that the presence of l/l will facilitate emotion regulation in the positive resting Fads group.

(Hypothesis 8) There will be a gene-environment interactive effect such that the positive relationship between state Fads and emotion regulation will be facilitated by the presence of l/l.

(Hypothesis 9 & 10) The same gene-environment interactive effect described in hypothesis 7 & 8 apply to the val/val carriers of the COMT gene

Limitations

Because of lasting neuroendocrine influence as cited above, we choose to forego counter-balancing of the order of conditions as we ascertained that once subjects were negatively aroused humoral effects would confound the lower levels of arousal during this lengthy task (mean task duration ~ 1.25 hours). Additionally, we kept the tasks in the same order for the following considerations: 1-because participants set their own level of TENS and 2- because TENS is mechanistically different than open-ended-shock and is in fact utilized clinically because habituation to the initially painful stimuli is known to occur.[83] In light of these factors (limitations) we concluded that if habituation was to occur it would be less

confounding were it to happen during the same task. As arousal measures were not significant for the spatial shock/threat of shock condition it seems these considerations did in fact manifest. Therefore, a limitation of the study is that verbal vs. spatial tasks at any level of analysis may not be compared and as such this study is not able to contribute to the literature concerning the circuitry or mechanisms at work that dissociate the inhibition of negative affective influences during spatial vs. verbal working memory task.[22, 50, 84-85] This description also serves as explanation for why state Fads did not predict emotion regulation or behavioral performance outcomes in the shock/threat of shock condition during the spatial task (arousal markers significantly lower). Lastly, because of the high levels of consistency between psychophysiological, self-report, known neuroendocrine effects and the documented anxiety induced by shock/threat of shock, order confounds are seen to have minimal influence on the interpretation of the noted results of this study.

Chapter II: Review of Literature

Introduction

The review of literature in chapter II is subdivided into eight sections. The first section highlights the relationship between arousal and performance with a call for the inclusion of cognitive and affective neuroscience in order to elucidate potential mechanisms underlying the relationship between these variables. The second section overviews basic concepts of the measurement of brain activity (electroencephalography – EEG). This overview is followed by illustration of its use during skilled psychomotor performance in an attempt to demonstrate the utility of the cognitive affective neuroscience approach to human performance. However, most of the previous studies in this area of research failed to consider the impact of emotion on performance. Therefore, section three introduces theories of, and describes the impact of, emotion on cognitive-motor and cognitive processing and its successful regulation/integration with said processes. The fourth section reviews the current neuroanatomy of the circuitry of emotion, with particular emphasis on fear, and the important role of the frontal lobes in the regulation and integration of emotion with cognition and motivation. Section five specifically focuses on the relevance of frontal asymmetry to emotion and human behavior, the frontal asymmetry difference score (Fads) metric, its history of associations with emotion regulatory processes and the debate concerning the state vs. trait nature of frontal asymmetry. The sixth section overviews the genetics of two single nucleotide polymorphisms (SNP) with known associations to dysfunctional emotion regulation. Section seven briefly outlines the

challenges surrounding the induction of stress in the laboratory. Finally, section eight sketches the programmatic approach (examination of EEG markers of cortical dynamics under increasing levels of arousal/stress) implicit in the design of the two studies included in this document.

Arousal and Performance Relationships

Cognitive-motor performance demands appropriate levels of arousal/motivation for successful execution. The inverted-U theory of arousal/performance claims that the specific demands of a task dictate the adaptive level of arousal. For example, power lifting requires very high levels of arousal as it is a gross motor skill, whereas performing an intricate surgical operation calls for controlled and effectively managed (i.e., typically lower or moderate) levels of arousal. The integration of emotion, cognition, and motor control processes in accord with adaptive goals is one of the more complex and demanding challenges of human performance. This coordinated action between the different domains of neurobiological processes is particularly challenging under high levels of stress, such as confronted by 1st responders, emergency/surgical medicine and police, military and rescue operations personnel. The insights gained from investigations of such groups also applies to other realms of more routine cognitive and motor performance in settings such as sport, job and academic achievement, public speaking, etc. Colloquialisms such as, "she made it look easy" are often applied to highly skilled athletes after successful achievement of difficult and multi-dimensional challenge. High volumes of deliberate practice result in refinement of critical cortical and sub-cortical processes (Angel, 1976; Black & Greenough, 1986) and interconnectivity

(Bell & Fox, 1996; Hatfield et al., 2004). The emergent networks within the CNS provide a necessary backdrop (dissociable - parallel circuitry) to the rapid and necessarily fluid circuits involved in moment-to-moment decision-making and movement execution during "performance under pressure." Disruption of cognitive/cognitive-motor performance during psychological stress is most likely found in the interactions between the involved neural processes (e.g., motor planning and attention processes).

The inverted-U model of arousal-performance provides a fundamental explanation of the impact of emotion on human performance. Accordingly, one must maintain an appropriate level of arousal (motivation/emotion) as pertains to the specific demands of task. Low levels of arousal are associated with relatively poor performance. Furthermore, arousal is positively related to performance up to an optimal point, beyond which it progressively declines. However, such a simplistic notion is devoid of mechanistic explanation and fails to outline how the complex processes in the brain and body, which change with arousal, influence the quality of performance. While at the gross behavioral level of analysis this synchronization of 'effort' to task appears straightforward, the complexites of brain function necessary to "make it look easy" are daunting. New work on attention (Hedden & Gabrieli, 2006) reveals that lapses of attention may be the product of failure to deactivate task-irrelevant brain networks, that themselves may be responsible for an adaptive (in terms of energy conservation) baseline or default mode (Gusnard & Raichle, 2001). This failure to disengage the default network under conditions of stress could introduce "noise" into the brain processes associated with skillful and adaptive

behavior, resulting in unintended influence to the working muscles and impaired performance. Thus, the task irrelevant processes interfere with the adaptive circuitry and intended processes responsible for high quality cognitive-motor performance. Optimal performance is typically characterized by conservation of energy and efficient metabolic processes in the various systems of the body such as the neural and musculoskeletal (Hatfield et al., 2004). As will be discussed later, this notion of economy and how it is disrupted by psychological stress is reflected at many levels of analysis, which will be discussed in Study 1 and Study 2. Kandel et al.(2000) speaks of "letting the subcortical circuitry of motor programs run without cognitive interference," This goal is easier said then done, especially in the face of the typically complex and highly demanding context of athletic performance.

Based on Yerkes & Dodson's (1908) classic study, Arent and Landers, 2003, recently conducted a test of the inverted-U theory as it has been questioned by a number of researchers (Hanin, 2001). They observed reaction time (RT) latencies to a simple attention task over a broad range of physiological arousal by assessing RT at while participants pedaled at various levels of resistance offered by a cycle ergometer. Importantly, they did note a classic curvilinear relationship between arousal and RT such that latencies progressively shortened as physiological arousal increased followed by a progressive increase at the higher levels of exertion. The finding supports and reinforces the basic relationship between arousal and performance, but illustration of this linkage is woefully inadequate in terms of explaining how and why performance changes (particularly more complex cognitive-motor processes) under varying conditions of arousal It is worth noting that in

research investigating the cellular correlates of learning, appropriate levels of stress hormones such as cortisol enhance learning and memory till a certain threshold (as defined by the inverted-U) at which point learning and memory are impaired (Kim & Diamond, 2002). In the present dissertation the analysis of cerebral cortical dynamics during the pointing task (Study one) revealed alterations in cortico-cortical communication and regional activation based on EEG coherence and spectral analyses, respectively, that offer explanations of how (and why) a moderate level of arousal could indeed enhance cognitive-motor performance (kinematics) of a visuomotor aiming task The usefulness of such a cognitive neuroscience approach, relative to traditional behavioral assessments of the arousal-performance relationship (e.g., self –reported state anxiety) is that it enables the assessment of underlying processes that can provide more information as to why behavior changes. Of course, such assessment must be conducted within meaningful theoretical frameworks. The purpose of Study 2 was to extend beyond Study 1 and investigate the role of the frontal cortex and genetic factors in the mediation of performance under pressure. More specifically, performance variation during cognitive challenge was explained by consideration of the frontal – limbic circuitry (as assessed by frontal EEG asymmetry) and relevant genetic factors in emotion control. The case is developed below that left frontal activation, which is indicative of effective arousal management, in conjunction with specific genetic influence will enable successful emotion regulation and superior performance under psychological stress (i.e., induced by negative emotion-eliciting stimuli and electric shock). Such an approach provides an additional attempt to

advance beyond the traditional notions of the inverted-U theory and explain performance under conditions of stress and emotional challenge.

EEG & the Cortical Dynamics of Skilled Performance

In order to initiate the cognitive neuroscience approach to emotion and human motor performance, an overview of brain electrical activity and the findings from its employment during motor performance are overviewed here. Human brain electrical activity (electroencephalography, EEG) was first recorded and subsequently published by Hans Berger in 1929. The signal is collected from the scalp and recorded as a time series with amplitude on the y- and time on the x-axes. Modern methods of EEG almost exclusively involve analog-to-digital conversion methods in which the analog signal is typically sampled between 256 & 2048 Hertz and band-passed between direct current and 100 HZ to accomplish the conversion. Contemporary study of human brain function employs EEG as a widely accepted objective measure to which biobehavioral markers of cognitive and/or motor performance can be related. The conjoint efforts of biology, psychology, electrical and computer engineering in the field of neuroscience have greatly enhanced the technology surrounding signal acquisition and processing and stimulated great flexibility in experimental design. The acquired signal is thought to be the result of dynamic fluctuations and interactive processes between assemblies of neurons spatially distributed in complex networks. (Nunez & Srinivasan, 2005). Additionally, the signal is believed to be derived from rhythmic firing of radially-oriented neurons (post-synaptic potentials) situated in cortical tissue (Davidson et al., 2000). It has been shown that anywhere from 2-6 cm^2 of neural tissue is needed to generate the

signal acquired at the scalp (Nunez & Srinivasan, 2005; Tao et al., 2005). EEG affords the researcher a millisecond level of temporal resolution and as such provides measures of relevant biobehavioral correlates of brain activity that may be confidently entered into statistical analyses in service of forming meaningful inference regarding human brain function.

The causal nature and functional relevance of brain oscillatory activity continues to accrue much support (Nunez & Srinivasan, 2005; Pfurtscheller & Lopes da Silva, 1999; Sejnowski & Paulsen, 2005). Alpha oscillations have been successfully used to derive relative levels of brain activation within well-defined experimental paradigms (Davidson et al., 2000). Amplitudes within the alpha frequency (8-13 Hz) have been inversely correlated with local processing. Thus higher amplitudes are used to denote elements of readiness and attention, but a lack of task engagement (von Stein & Sarnthein, 2000).

EEG studies of skilled athletic performance support a model in which skill acquisition is significantly correlated with specific reductions in regional brain activity and decreases in networking between task-irrelevant and task-relevant components of the motor loop (Hatfield et al., 2004). In general, EEG alpha power is inversely related to local cortical activation. Activation in the left temporal lobe (T3) has typically been examined during the performance of self-paced motor tasks (e.g., archery, golf putting, and target shooting tasks) as phenomenological reports of superior performers (i.e., athletes) reveal that they suppress verbal processing and analytical processes during task engagement. The activity of the right temporal lobe

(T4) is also typically examined during such studies in light of the reliance on visual-spatial processing (Cohen, 1993).

Hatfield et al. (2004) summarized the main findings from these studies and a number of additional relevant investigations that support the notion of refinement of cortical processes with the development of psychomotor skill: 1- Expert performers, as compared to novices, demonstrate higher left temporal (T3) alpha power prior to trigger pull (Hatfield et al., 1982, 1984; Haufler et al., 2000); 2 - In a deliberate practice intervention, increases in alpha were observed with extended practice as recorded from both the T3 & T4 sites (Kerick et al., 2004); 3 - DiRusso et al. (2003) observed faster and less variable saccadic trajectory toward target between experts and novice in a standard vs. distracter task. Additionally the researchers employed an intervention in which controls were trained, subsequently resulting in a similar decrease in duration and variance of visual saccadic trajectory. 4 - Using EEG coherence (i.e., coherence is a measure of the linear correlation between the power spectrums obtained from two separate EEG recording sites. Higher coherence implies communication between the regions involved, while low implies orthogonality). Deeny et al. (2003) grouped skilled marksmen into two cohorts: one representing experienced shooters who perform well under the stress of competition and those who perform below the level they display during practice. Both groups showed the same coherence patterns between all measured regions and the motor planning region (FZ) except T3. Coherence between the verbal associative region and the motor planning region was significantly reduced in the accomplished competitor group. 5 - In a recent emotion eliciting paradigm Chen et al., 2005, showed similar increases in T3-FZ

coherence in practiced dart throwers under threat of shock. 6 - In a landmark study Bell and Fox (1984) observed significant changes (i.e., reductions) in coherence between pre crawling, initial crawling and experienced crawling in human infants. Based on developmental trajectories of connectivity in juvenile brain, expected increases in coherence were seen between motor and visual regions as the infant went from pre-crawling (low coherence between visual-motor as neuroanatomy was not developed) to notably high levels during early crawling (this is when the trial and error of learning is heightened) to an analogous streamlining of circuitry (as measured via coherence) as the experienced crawler "gets it down to a science." These exemplars convincingly support the unifying principle of economy of resources (Hatfield & Hillman, 2001). However, a major gap in this area of research is the failure to consider the impact of emotion on the cerebral cortical dynamics.

The Impact of Emotion and its Regulation

Traditionally, emotion has been thought of as having a negative influence upon cognition, "if you want to see this clearly you must take your feelings out of it," is an often repeated piece of advice. In stark contrast a large body of work from Damasio and colleagues (Bechara et al., 1997,-2000 & Damasio, 1994,-96), has shown that rational thought (i.e., cognition) functions at significantly more adaptive levels when integrated with emotion. The 'Iowa Gambling Task' assesses the ability of subjects to choose a long over short term benefit, patients with lesions in affective regions of the brain perform significantly below the level of controls.

Another important theory of emotion by Rolls (2005) defines emotion and outlines its functions:

1-“emotions are states elicited by rewards and punishers, that is by instrumental reinforcers and have particular function,

2-emotions function as a way to provide a mechanism for genes to influence behavior in a brain that evolves by gene selection, genes specify the stimuli or events that the animal is built to find rewarding or punishing, (i.e., reinforcing),

3-so genes specify the goals for actions but not the actions themselves, as that would be genetically expensive. This is consistent with Darwinian theory in that genes specify reinforcers, i.e., goals for action that will increase the fitness of the gene-emotion may be thought of as states elicited by goals (reward-punishers) and motivation may be thought of as states elicited when goals are being sought

5-***emotions are at the heart of brain design.***”

Historically, a behavioral perspective has dominated studies of emotion regulation. However, its exploration via the biobehavioral approach of affective neuroscience has added both depth and breadth. The resultant corpus of work has revealed much about the neural underpinnings of emotion regulation (see Davis, 2007, Quirk-2006, Quirk & Mueller, 2008 and Phelps & LeDoux, 2005 for recent reviews). Through examination of both its unconscious (automatic) and conscious (deliberate) mechanisms, two major sources have come to dominate the work in emotion regulation. First, work from animal research at multiple levels of analysis has utilized fear conditioning paradigms (Ledoux, 2003, Maren & Quirk, 2004, Pare et al., 2004 & Rodrigues et al., 2004) while manipulating various temporal, behavioral and molecular elements of extinction (the most fundamental form of emotion regulation). The other major source derives from human imaging work (Blair

et al., 2006,-7 Dolcos et al., 2004,-6,-8, Egner et al., 2007, Lee et al., 2008, Luo et al., 2007 & Ochsner et al., 2002,-4,-6,) that follows one of two basic paradigmatic paths. In the first model participants actively suppress or enhance emotional experience elicited from memory and or affectively laden stimuli such as film clips or photos. While in the second model participants are presented similar affective probes along with more potent stimuli such as threat of shock or shock and are asked to regulate emotional influence/interference during challenging working memory tasks.

Recently, these separate bodies of work have been integrated to glean valuable insights. The most accepted outlines are as follows: for automatic regulation, the amygdala is widely agreed upon to initiate the arousal associated with fear/anxiety. Its putative control centers (i.e., the brakes) that manage the level of activation in the amygdala appear to be in ventromedial Prefrontal Cortex (vmPFC) and the subgenual Anterior Cingulate Cortex (sACC). The Dorsolateral (DLPFC) and Ventrolateral prefrontal cortex (VLPFC) interact through multi-sensory receiving and reward evaluation zones in the Orbitofrontal Cortex (OFC) to enlist vmPFC-ACC nuclei that have bidirectional connections with amygdala through which affect/arousal may be up or down (more typical) regulated in service of goal-directed behavior. However, a recent opinion paper from Pessoa (2008) has organized substantial empirical support and compelling conceptual logic in an effort to fundamentally change (improve) this outline and future study within the field. The paper calls for an end to the strict division of emotion and cognition. This position is in agreement with others, such as LeDoux (2002), and due to substantial inconsistencies noted across both the temporal and spatial span of its development and its tautological usage, it is suggested that

even the label ‘limbic system’ be eliminated. According to Pessoa’s view, the traditional perspective that emotion and cognition are distinct should be replaced by an integrated perspective that recognizes the intricate and highly connected systems with components described as central and provincial hubs to denote both their long and short range roles in not one but multiple streams of information processing. This view provides an insightful framework in which these same complex networks interact (regions may share involvement with the same neural computation or they may separately be involved in additional computations with other regions) to support adaptive behavior while the distinction between affective and cognitive processes moves along a three-dimensional gradient where one or the other may dominate but at no time are they orthogonal. Integration of cognition, emotion and motivation becomes a higher order goal capable of subsuming the much sought after two-headed dragon of double dissociations and most of its single location-single function cousins. Examining the integration of locale(s) and function(s) and their corresponding synchronization in time (phase synchrony) is shown to resolve certain inconsistencies in current models and provide a broader and more powerful understanding of human brain function. This work supports such a framework and aims to contribute empirical evidence for the integration of cognition and emotion. The networks in which emotion and cognition are successfully integrated to produce adaptive moment to moment decision-making are the very circuits that must interact with the stable, aforementioned circuitry of skilled cognitive-motor performance.

Neuoroanantomy: Role of the Frontal Lobes in the Integration of Emotion & Cognition or, "What is connected to the tissue beneath the electrodes that acquire the signal used to compute the frontal asymmetry difference score (FADS)?"

Empirical support has accrued for current theories of emotion (Damasio, 1994) derived in part from the James-Lange tradition in which central representations of bodily states differentiate 'feelings/emotion" from cognition. To briefly summarize (for an in-depth account of the flow of information through the circuitry initiated by autonomic/ visceral & nociceptive impulse see: Craig, (2004,-5) & Critchley, (2005): visceral information (autonomic-homeostatic-includes pain) traverse vagal afferents to the nucleus of the solitary tract (NTS-parasympathetic) or lamina 1 spinothalamic tracts (sympathetic) to then bypass (primate adaptation) brainstem and midbrain nuclei and converge in the diencephalons. Various thalamic nuclei advance the information stream to cortical locations such as ACC, posterior, mid-(may enter amygdala from here) & anterior-Insula before entering the OFC (Bechara et al., 2000, Rolls, 2004,-5, Rolls & Kringelbach, 2004) and from there to the DLPFC for decision making (Fuster, 1997, Gray et al., 2002, Pessoa, 2008, Pizzagalli et al., 2005 & Rolls, 2004).

Re-representation of homeostatic signals within the anterior Insula allows for conscious awareness of the bodily states that are proposed to be the "stuff of emotion" (Craig, 2004,-5, Critchley, 2005, Damasio, 1994 & Pribram, 2003). Cortical and subcortical nuclei in amygdala, hippocampus, ACC, vmPFC and Insula exert executive influence over hypothalamic and brainstem centers of autonomic control (Craig, 2004,-5, Critchley, 2005 & Damasio, 1994). The hypothalamus

monitors the internal milieu, while correlated activity in its Paraventricular nucleus (PVN) initiates the release of corticosteroids, the humoral agents of the flight or fight response (Berntson et al., 1991, Critchley, 2002,-5, Joels et al., 2008 & LeDoux, 2002). Brainstem centers/nuclei of autonomic control (both sympathetic & parasympathetic) are instrumental in the release of powerful neuromodulators that directly influence sensory discrimination and mediate synaptic mechanisms intimately involved in the processes of attention, learning, memory and arousal/affect (Anderson & Phelps, 2002, Glascher et al., 2007, Kim & Diamond, 2002 Kirkwood, 2000 & Phelps & LeDoux, 2005). Thus, the aforementioned descending cortical and subcortical structures found to impact hypothalamic and brainstem centers of autonomic activity find themselves in the highly influential position of being able to up and down-regulate affect/emotions in service of its interactions with cognition and motivation. This up and down regulation may be initiated through evaluation of sensory stimuli (automatic-amygdala pathway), or via the influence of executive control centers most likely found in dorso- and/or ventro- lateral PFC (conscious-cognitive) or through the contents of long-term memory-which may affect both the automatic and conscious pathways (Kalisch, 2006 & Ochsner, 2002,-4,-5).

Rigorous work on fear conditioning accomplished by pairing auditory stimuli with footshock (animal models) (Ledoux, 2003, Maren & Quirk, 2004, Pare et al., 2004 & Rodrigues et al., 2004) has established the amygdala as the central player in most aspects of fear-modulated learning and memory (attention, encoding, consolidation, retrieval & reconsolidation).

The amygdala (of central hub status (Pessoa, 2008 & Sporns, 2007) appears to derive the affective salience (Ghashghaei et al., 2007) of sensory stimuli, amplify relevant aspects of such stimuli through initiation of CNS arousal mechanisms and deliver this enhanced (Anderson & Phelps, 2002, Glascher et al., 2007, Kim & Diamond, 2002 Kirkwood, 2000 & Phelps & LeDoux, 2005) package to the ACC/PFC. The PFC (DLPFC) then incorporates these privileged (Davidson et al., 2004, Ishai et al., 2004) messages in order to adaptively exert executive control over goal-oriented behavior (Ghashghaei et al., 2007 & Bechara et al., 2000).

The signals used to compute Fads are acquired from scalp electrodes positioned directly above areas of the DLPFC (Pizzagalli et al, 2005). Yet efferents from ACC & vmPFC are by consensus (Ghashghaei et al, 2007, LeDoux 2002-4-6, Quirk 2006, Pare et al., 2004, Phelps & LeDoux, 2005 & Vogt, 2005) the source of the connections that enter the amygdala to exert inhibitory influence over CE output, directly involved in upregulation of autonomic arousal. Very recent evidence from non-human primate studies (Ghashghaei et al., 2007) shows the amygdala to be connected to every area of the PFC; however some areas (BA 10) have minimal connections while others are heavily connected. BA 24 & 25 (ACC or rMCC (Vogt, 2005) and sACC or vmPFC respectively). BA 24 and 25 are predominately senders (able to up or down-regulate amygdaloid activity), while caudal Orbitofrontal areas are predominately receivers

DLPFC is not known to have direct connections to sACC or vmPFC. However, DLPFC is bidirectionally connected to the OFC which in turn is connected to the ventromedial sectors mentioned above (Bechara et al., 2000, Pizzagalli et al.,

2005 & Rolls 2004). It is suggested that OFC nuclei receive multimodal sensory and limbic afferents from posterior parietal cortex, Insula, vmPFC and amygdala (Critchley 2005, Rolls, 2004, Yamada et al., 2006 & Yamasaki et al, 2001), which are then integrated to compute reward values (contingencies), the information stream then continues to DLPFC wherein both reward value and behavioral decisions are computed/represented (Pizzagalli et al., 2005, Rolls, 2004 & Sakai et al., 2002 & Wallis & Miller, 2003). The DLPFC (& VLPFC) is often shown to be the site of cognitive control (Blair et al., 2006,-7, Dolcos, 2004,-6,-8, Lee et al., 2008, Luo et al., 2007, Ochsner, 2002,-4,-5, Pessoa, 2008, Sakai, 2002 & Sporns, 2007). Further, Quirk et al., (2006), posits frontal regions, BA: 10, 11, 25, 32, 47 and possibly parts of 24 & 33 as the regions encompassing, 1-retention of extinction memories (simplest form of emotion regulation), 2-suppression of undesirable emotion and 3-cognitive reappraisal of emotion, while significant fMRI research has demonstrated relative agreement with this and additionally has posited BA 6/9 as having a functional role in challenges of information load, and areas BA 45- 47 to have roles in the inhibition of interference (Blair et al., 2006,-7, , Dolcos et al, 2004,-6,-8, Lee et al., 2008, Luo et al., 2007, & Ochsner et al., 2002,-4,-5).

The PFC comprises approximately one-quarter of the cerebral cortex (Johnson et al., 2002). The vast number of computations it is involved with is only briefly sketched above. Further, pivotal frontal functions include: 1-fronto-parietal networks have been extensively associated with attentional processes (Compte et al., 2000, Gusnard & Raichle, 2001 & Yamasaki, 2002) 2-as have fronto-striatal circuits with motivation (Akil et al. (2003) & Pessoa (2008)). In addition to its ability to directly

up and down-regulate brainstem, autonomic and hypothalamic nuclei associated with arousal (Critchley, 2005, Ghashghaei et al., 2007, Joels et al., 2008 & Vogt, 2005), the vmPFC is thought to innervate both the VTA and Substantia nigra (SN)) and may be capable of influencing the balance of both frontal and striatal release of dopamine known to be involved with motivation, movement, reward and frontal lobe executive function (Akil et al, 2003). Finally, Basal Forebrain (BF) cholinergic release known to affect attention, sensory encoding and learning (Kringelbach & Rolls, 2004 & Pessoa, 2008) can be added to the list of influential nuclei functionally connected to the PFC. Thus, the prefrontal cortex may exert executive influence over virtually all prominent and widespread neuromodulatory systems affecting the cerebral cortex. Multiple PFC regions and the networks in which they are embedded are intimately involved with the integration of emotion, cognition and motivation and are known to be functionally connected (Damasio,1994, Davidson, 2004, Ghashghaei et al., 2007, Kringelbach & Rolls, 2004, LeDoux, 2002, Ochsner & Gross, 2005 Pizzagalli et al., 2005, Rolls, 2004,-5& Vogt, 2005) to the sustained firing (Adcock et al., 2000, Dolcos et al, 2008, Fuster, 1997, Rolls, 2004 & Sakai et al., 2002) necessary for the maintenance of short-term memory trace found in the DLPFC, the putative source of the signal that gives rise to the Fads.

Considerable evidence has amassed supporting functional lateralization in regards to affective processing (Allen & Kline, 2004, Bechara et al., 2000, Craig, 2004, Critchley et al., 2004, Critchley, 2005, Davidson, 2004, Murphy et al., 2003, Ochsner et al., 2002, Phan et al., 2004 &.Pizzagalli et al., 2005). To very briefly sketch this literature: left frontal activations are dominated by approach behaviors and

positive valence, while right frontal activation is associated with withdrawal behaviors, negative valence and arousal. Important new work, see Craig, (2005), provides a solid foundation for this lateralization, which the author roots in the hierarchical neuroanatomy and paired opponent processing of the autonomic nervous system. The core of Craig's 2005 model reflects principles of organismic energy management in which energy enrichment is associated with the left forebrain and energy expenditure is associated with the right forebrain. A prototypical example of this comes from empirical evidence showing that dominant efferent innervation of cardiac parasympathetic electrophysiology derives from left hemisphere control centers while the opposite holds for sympathetic efferents (Craig, 2005, Wittling et al., 1998a & Wittling et al., 1998b). These noteworthy results further solidify the notions of lateralization of frontal function, in regards to emotion and cognition interactions, provided by thirty years of distinguished EEG/neuroimaging study by Davidson and colleagues.

Frontal Asymmetry

The paragraphs above speak to the vast network based complexity of brain function and the multiple levels of analysis necessarily applied to the onerous task of advancing our scientific understanding thereof. Yet, another level of complexity must be stirred into the hierarchy and that is the idea of individual difference. Davidson, 1999 has coined the term 'affective style' to describe one's predisposition to act a certain way during a range of emotional challenges. An example might be: predicting the wide range of individual response to the challenge of public speaking via an agreed upon index of predisposition. Historically, the science of individual

differences has grouped people based upon psychological evaluation techniques such as self–report on valid and reliable questionnaires and or on their performance of standardized, ambiguous tasks (Endler, 1997 & Mischel et al., 2002). Currently, cognitive-neuroscience assesses theory-driven combinations of biological markers (genes, molecular processes & psychophysiologic response, including BOLD) during various cognitive-emotional challenge (along with self-report) in order to better understand individual differences at multiple levels of analysis and across varied situations. A important example of this is found in the Etkin et al, 2004,[58] human imaging (fMRI) study in which unconscious activation of the basolateral amygdala to fearful stimuli was found only when individual differences in trait anxiety were considered as a grouping variable.

Employed as a marker of individual difference, the EEG frontal asymmetry difference score (Fads) is derived via the following sequence of computations: 1-EEG signal is acquired from frontal homologous pairs of electrodes (F3, F4), 2- the signal is transformed from the time domain to the frequency domain via Fourier transform or an analogue thereof, 3- the power in the alpha frequency bandwidth (8-13 Hz) is averaged over the frequency band and calculated during the time period of interest (often a 4-minute eyes open and 4-minute eyes closed 'baseline' period) from which a single mean is computed. Typically participants are grouped as either a positive or negative Fads carrier and that delineation is entered into various statistical analyses as either a grouping or a predictor variable.

As a viable metric of the approach-withdrawal dimension of emotion regulation, the EEG derived Fads has established considerable support (Davidson

2004, Allen 2004). Individuals with higher positive vs. negative Fads fare better at the management (resilience) of negative emotional stimuli (Jackson et al, 2003). The bulk of this research has been conducted with a positive resting (baseline) Fads as a predictor of, for example: Jackson et al 2003, partitioned subjects into negative and positive resting-Fads groups and found lower eyeblink startle- electromyography (EMG) magnitudes in response to fear elicitation for those with positive resting-Fads. Other important examples include: higher immune titers (Rosenkranz et al, 2003), lower basal cortisol measures (Kalin et al, 1998), lower cerebral spinal fluid (CSF) measures of corticotrophin releasing factor (CRF), (Kalin et al, 2000), decreased facial EMG during affectively negative stimuli presentation after neuro-feedback increases of positive-resting-Fads (Allen et al, 2001), higher behavioral activation scores (BAS) & lower behavioral inhibition scores (BIS) Coan & Allen 2003) and decreased amygdalar activation to affectively negative stimuli (Schaefer et al, 2002). However, studies aimed at understanding the neural instantiation, time course and electrophysiologic correlates of the state measure of the processes responsible for this metric are rare (Coan & Allen, 2006). That is, the majority of investigations have examined the correlates of resting Fads as described above, while far fewer studies have examined the psychophysiologic processes associated with the state (phasic/situational) Fads

Trait measures of Phasic Phenomenon & the 'Capability Model'

One of the central problems in measuring emotion regulation via the assessments derived from trait measures such as self-report (applicable to trait), genotype and resting Fads is that emotion regulation itself is a phasic/situational

process. Thus, state measures of its neural correlates may in fact be more predictive of trait tendencies, if one accepts the notion that individual differences are more productively measured within specific contexts (situations), (Coan et al, 2006). Anecdotally, most of us have experienced or engaged in conversation in which statements such as "she is a pretty good most of the time but a real clutch player in the post-season." This situational view of disposition (or more accurately is it a view of one's 'capabilities') has found support in the literature (Mischel et al, 2002). A situational framework that has been well-tested is Endler's, 1997, "multi-dimensional interactional model," which highlights person-situation-environment relations/integration as contrasted to more typical trait measures of personality described above. Coan et al. 2006, have proposed a 'capability model' for the individual differences described by the Fads (for an in depth assessment of this model see Coan et al, 2006), in which they state, "while the dispositional model of Fads aims to measure individual approach versus withdrawal disposition *regardless of situation*, the capability model aims to measure the degree to which individuals are capable of approach versus withdrawal responses, or, importantly, of inhibiting those responses *depending on the demands of the situation*" (Coan et al, 2006, p.198). In this important study they highlight previously inconsistent results obtained using resting measurements of emotion regulation via the Fads metric such as: reference scheme error, lab setting & experimenter effects, situational changes in subjects daily routine (i.e., just failed an important exam) and negatively characterized affect associated with relative left frontal activation. (Hagemann 2002, -4,-5). Remarkably Coan et al. 2006, found: 1-Individual differences in Fads are more marked during

state vs. resting tasks, 2-individual differences during state vs. resting conditions are less susceptible to artifact introduced by the problems outlined above such as reference scheme and 3-state measures of Fads are more reliably correlated to self-reported measures of affective personality characteristics. Perhaps, the strongest finding in their study was, using a G-theory model and obtaining Fads across five different emotion inductions and at rest, that 50% of the variance in Fads was explained by an individual by condition interaction, which they put forth as solid preliminary evidence in defense of a 'capability model' providing a more reliable explanation of the attributes indexed by the Fads.

By definition a dimension of a complex and distributed process/system such as emotion should find utility in more than one category of emotion (Craig, 2005, Harmon-Jones, 2003, Murphy et al., 2003, Phan et al., 2004 & vanHonk & Schutter, 2006, &). A partial goal of the studies cited above has been to uncover the 'primitives' of emotion. Dimensions such as approach/withdrawal, positive-negative valence and semantic vs. personal & affiliative vs. personal relevance have been supported in a number of studies (Allen & Kline, 2004, Craig, 2005, Davidson, 2004, Gable & Harmon-Jones, 2008, Harmon-Jones et al., 2006, Murphy et al., 2003, Phan et al., 2004 & vanHonk & Schutter, 2006). Agreement on either what constitutes a primitive and or how these dimensions (subroutines) may in fact be combined to account for the abundance of categories of human emotion has not been reached. Confounds have been uncovered in regards to seemingly straightforward emotions such as anger. Typically categorized (or dimensionalized) as an example of a negative emotion, anger has been shown to be associated with approach behavior (Harmon-

Jones, 2003,-6, von Honk& Schutter, 2006). Approach behavior is thought to positively correlate with positive valence (Davidson, 2004). This conundrum has been partly resolved by logic which claims that anger in the context/service of changing an 'injustice' ("you overcharged me for this service, now fix it") does in fact fit within the positive valence dimension. Much progress in cognitive neuroscience has been made parsing or identifying dimensions into which broader categories may be decomposed. If similar logic is applied here then most of these paradoxes dissolve. Humans are well known for feeling more than one emotion simultaneously, thus even broad categories of emotion may be combined to produce ever more complex constructs of emotion. The keynote here is that the combinatorial possibilities of the dimensions should not be decided by logic derived from past perspectives but from both past and empirical evidence yet to be revealed. Withdrawal is typically assigned a negative valence, however, if anger (in certain contexts) is considered both approach-oriented and positively valenced, then surely withdrawal should within a dimensional model of emotion and in certain contexts be considered to have positive valence. Few would argue that removing oneself physically and socially from harm's way is an adaptive response. Thus, adaptive withdrawal simultaneously supports dimensional models of emotion and steers us toward the utility of a capability model (interestingly, a piece of the neurobiology of getting out of harm's way may have been elucidated in animal research as rodent's expecting shock and not receiving it, demonstrated opioid release from PAG nuclei, Quirk, 2006). Lastly, one of the limitations of this study and the current literature in terms of understanding the neural correlates of Fads is: at this point in time and in regards to the laboratory activities

participants have engaged in, the opportunity to withdraw on a trial by trial basis has not been offered and therefore constrains the inferences drawn regarding withdrawal behavior as psychophysiologic measures surrounding the actual decision/execution of withdrawal have not been acquired.

Genetic Modulation

Logically one might infer that the predispositional measures of resting-Fads and genetic influences acting within the emotion regulation circuitry should correlate. However, resting measures of Fads have shown weak heritability, to summarize: 1-Anokhin et al, 2006; No heritability of Fads, 2-McDhomhail et al. 1999; females .35 & males .21 (using Falconer's estimate), 3-Coan et al, 2004; .22 females and not heritable in males, Smit et al, 2007; divided groups into > 35 years old (mean = 49.4) and < 35 years old (mean = 26.2), only found heritability in the younger cohort, males .32 & females .37. Again, it is our belief that by incorporating the as of yet unknown but appropriate combination of resting and state-Fads markers, that measures of heritability may in fact be stronger than they now appear.

Individual differences are known to be associated with genotypic variation. In the last decade, association of frontal lobe function and dysregulation of emotion with specific allelic variants has yielded fruitful results. Key studies in imaging genomics (Hariri & Weinberger 2003, Winterer & Goldman 2003, Meyer-Lindenberg et al, 2006) have linked certain genotypes to poor emotion regulation/high anxious phenotypes. The single nucleotide polymorphisms (SNP) of both the Serotonin Transporter (SERT) and Catechol-oxygen-methyltransferase (COMT) genes have been investigated in some detail. Through the employ of different neuromodulatory

mechanisms, allelic variants of both of these SNPs have been implicated in dysregulation of affective processing.

What is COMT and What has been Associated with COMT?

COMT was the first gene discovered (1950's) to have a role in frontal lobe function, the gene codes for an enzyme involved in the catabolic metabolism (methylation) of the catecholamines-dopamine (DA), norepinephrine (NE) & epinephrine (EPI). The COMT gene on chromosome 22q11contains a G to A missense variant that is manifest by a methionine (met) to valine (val) substitution at codon 158 (val 158 met). The enzyme containing the met allele is labile at 37° C and thus has one-third to one-fourth the activity of the val allele. The COMT enzyme in most areas of the brain plays a secondary role to dopamine transporters (DAT) in the clearance of DA from synapse but DATs are absent in the frontal lobes, therefore PFC DA metabolism is heavily dependent on COMT (acts post-synaptically), the net result of the met allele is higher levels of PFC DA (of some interest is the fact that the met variant is absent from other primates), the effects are additive (Craddock et al, 2006).

The higher levels of frontal dopamine conferred by homozygous met status has been associated with better performance on WM tests (Goldberg et al, 2003), better PFC signal to noise ratios; less single trial variability in frontal P300's (Gallinat et al., 2003), and a more efficient physiology (less activation) coupled with better performance on an executive cognition task while measured via fMRI (Smolka et al, 2005). Thus, dopamine metabolism and neurotransmission within the human frontal lobes has been shown to critically impact cognitive function (Williams & Goldman-Rakic, 1995).

Smolka et al, 2005, note, "Given its disadvantages for PFC function, it is curious the val allele is highly prevalent (~50%) in various populations (Palmatier et al, 1999)." Many studies have contributed to the notion that val allele carriers may have increased emotional resilience over anxiety. An abbreviated list of the research to support this claim is: Zubieta et al, 2003--met carriers show higher sensory and affect ratings to nociceptive stimulation, Enoch et al, 2003--met carriers show higher levels of dimensionally measured anxiety, Woo et al, 2004 –met carriers show elevated associations with panic disorder and Smolka et al, 2005--met carriers show increased BOLD response to negative vs. positive emotional stimuli. To summarize, within the context of the human frontal lobes, met homozygosity is associated with increased cognitive function but decreased emotional resilience and val homozygosity is associated with the opposite.

What is 5-HTTLPR and What has been Associated with 5-HTTLPR?

5-HTTLPR (5-HydroxyTryptamine Transporter Linked PolymoRphism), is found in the 5' promoter region of the human serotonin transporter gene (SERT) located at the SLC6A4 locus on chromosome 17 (17q11.1-17q12), it spans 31kbp and contains 14 exons. A variable number of tandem repeat (VNTR) element was found in the second intron and a 44bp insertion/deletion polymorphism has been identified in the transcriptional control region upstream of the serotonin transporter gene The two common alleles, the short (s) and the long (l) confer variable tandem repeat sequences in the promoter region of SERT. The net result is an alteration in the level of serotonin transporter function, l-allele carriers have higher concentrations of 5-HTT mRNA and a two-fold greater 5-HT uptake compared to s/l or s/s carriers

resulting in a hypothesized higher level of 5-HT in the synapse of s carriers, s allele appears dominant (Hariri & Weinberger, 2003).

Serotonin plays a key role in brain development affecting both the development of serotonergic and glutamatergic (main excitatory neurotransmitter of cortex) circuitry. The amygdala and ACC have very high serotonergic innervation, with the ACC (BA 25) showing highest 5-HT receptor density in the human cortex (Varnas et al., 2004). Depression and anxiety have been correlated with serotonergic transmission in numerous studies (Hariri & Weinberger, 2003). The heritability of depression approaches 70% and anxious temperament has been correlated with risk for depression (Wong & Licinio, 2001). Carriers of the s-allele show heightened anxious behaviors relative to l/l carriers (Hariri & Weinberger, 2003). During perceptual processing of fear inducing stimuli, Pezawas et al., 2005, using fMRI, showed important correlations in 'functional connectivity,' within the key affect regulation feedback loop from the amygdala to the rACC to the cACC and back to the amygdala, with s-carriers having relative uncoupling in the first and third legs of this circuitry and higher TPQ measures of anxiety (the magnitude of coupling explained 30% of the variance in temperamental anxiety).

The structures and processes being examined in the imaging genomics research cited above are the very same to which the construct validity of Fads has been shown to reliably index. Thus, it is of interest to begin to access the association of these specific genotypes with the individual differences explicated by the Fads metric.

Laboratory Inductions of Stress/ Arousal

Key reviews (Dickerson & Kemeny, 2004 & Noteboom, 2001) of the long history of laboratory inducement of stress reveals that these attempts rarely reach levels of real world stress (as in military and/or medical emergency situations) . However, it conclusively states that elevated levels of arousal/stress are indeed attained in the laboratory environment. The take home message translated into layman's terms reads as follows: "throw everything you have at them." Examples of proven stressors are: 1-Shock/Threat of shock, excessive heat, cold presser, 2-Emotion, eliciting photos and Film Clips, 3-Audio Noise, 4-Social Evaluation and Competition, 5-Time pressure

IAPS is a series of pictures/photographs that have been empirically demonstrated to induce emotion within laboratory settings (Lang et al., 1999). IAPS has successfully been used in the scientific investigation of arousal/emotion for over a decade.

In laboratory research shock/threat of shock has been set apart as a rather specific generator of anxious arousal. It is further characterized as producing a 'clean' state of anxiety in which confounds as to the cause of arousal are minimal or non-existent (Greenwald, 1998 & Phelps et al., 2004) The eyeblink startle reflex has been shown to be a reliable indicator of anxious arousal and as such is fully characterized as an index of negative valence (Bradley et al., 1999, 2006, Cuthbert et al., 1996 & Lang et al., 1997). Increases in skin conductance indicate activation of the sympathetic branch of the autonomic nervous system, known to play the central role in general arousal (Critchley, 2005 & Andreassi, 2000). Corroborations of subjective

experience as recorded through valid/reliable measures such as VAS add credence to psychophysiologic measures of affective state (Bijur et al., 2001).

Programmatic Approach to 'Performance Under Pressure'

The purpose of our research is to elucidate EEG correlates of successful vs. failed attempts at the regulation of emotion in service of cognitive-motor/cognitive performance, so called 'performance under pressure.' Further, should these understandings reveal themselves; they will be employed in the design of various interventions. One of which; will be feedback of specific EEG signatures of emotion regulation to participants with the goal of enhancing their ability to integrate emotion and cognition in the service of performance.

Chapter III: Methods

Participants

A total of 63 volunteers were recruited during the Fall 2007 semester from the University of Maryland, College Park. From this pool of 63 volunteers, 32 were chosen for participation in the testing phase of the study. Selection was based on their Fads (described below), one group (16) contained subjects with a negative resting Fads, while the other group (16) contained subjects with a positive resting Fads. Thirty of the thirty-two participants were right handed and ipsilateral-eye dominant as determined by the Edinburgh Handedness Inventory (EHI); one was left-handed and another ambidextrous. Participants were free of any exclusionary health conditions as outlined via a Health Status Questionnaire, (HSQ). Included participants were paid $60 for taking part in the study.

In addition, all participants were asked to refrain from alcohol for at least 24 hours and from caffeine, nicotine and large quantities of food or water (>1 quart, sipping, snacking is fine) for at least 75 minutes before any psychophysiological testing began. On day one, screening day, all participants completed a University of Maryland Institutional Review Board (IRB) approved informed consent, the HSQ, the EHI, Spielberger Trait Anxiety Inventory (STAI), the Behavioral Inhibition & Behavioral Activation Scale (BIS/BAS) and the Positive and Negative Affect Schedule (PANAS).

Task/Protocol and Instrumentation

N-Back

Two separate two item N-back working memory tasks were employed. One task (verbal) presented a series of letters (4-6) and subjects were asked to decide if the target letter (different color than probe letters, probe-yellow, target-purple) was the same as the probe presented just prior to the last probe. The second task (spatial) was identical to the first but subjects were required to remember the location (one of 8 possible locations) of a white rectangle. Both visual stimuli for the two tasks were psychometrically matched (Baddeley, 2003).

IAPS

The international affective picture system (IAPS) is a well documented collection of photos that have demonstrated reliable elicitation of emotion/arousal. Photos include displays of various emotions: from fearful (bleeding, people being cut with knives) to neutral (a chair), to appetitive (appetizing food) (Lang et al., 1999).

TENS

Transcutaneous nerve stimulation (TENS), is the introduction of low levels of current (1-80 milliamps) from two to four electrodes placed over exposed skin (dorsal surface of right foot). It is typically used for therapeutic intervention for post-surgical-wound, chronic pain and or lower back pain Stimulation of larger diameter sensory neurons via the mild current blurs the pain signal delivered via the smaller diameter a- and c-fibers associated with the conduction of pain. However, the intensity of the TENS unit may be increased enough to cause moderate pain. In this study it was used at levels to incur brief but moderate pain (Johnson et al., 1991).

Protocol

Participants were seated in a comfortable chair (to minimize muscle artifact) approximately 48" away at eyelevel from a projection screen (48" x 36"), upon which all images were displayed using, InFocus., Wilsonville, OR, Video Projector, model-IN 24.

The testing session entailed three blocks (conditions), each consisting of 66 (33 each of verbal and spatial working memory (WM) task) stimulus-response trials. A single trial includes: 1-International Affective Picture System (IAPS) presentation, 2-2 bursts of White Noise (the 1st was delivered the last 50 ms of the image display and the 2nd was delivered 4 seconds later, just prior to the presentation of the 1st WM probe) , 3-N-back task (2-back), 4-Visual Cue, 5-Transcutaneous Electric Nerve Stimulation (TENS). (see Fig.1 for a graphical representation)

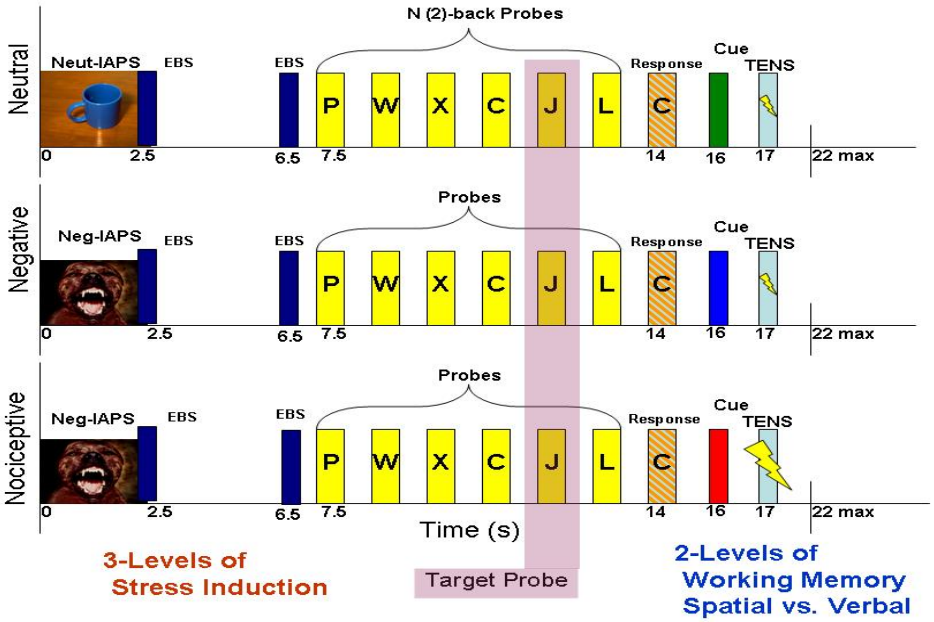

Figure 1

Graphical representation of the task protocol. All trials consisted of an IAPS presentation, then two blasts of white noise separated by 4 seconds, followed by the n-back task (2 back), then a visual cue, and ending with electrical stimulation. During negative and nociceptive conditions the IAPS picture was negative. Further, during only the nociceptive condition, the electrical stimulation was increased to a noxious level.

Participants completed two levels of the 2-back working memory task in three separate blocks of 66 trials each. Thirty-three Verbal and 33 Spatial N-back tasks were administered in sub-blocks during each condition/block. The task consisted of a variable-number (between 4 and 6) of consecutive probe letters (verbal) or rectangles in different positions in space (spatial) visually displayed at eye level followed by a target letter or position. Within each trial, the subject was required to indicate whether or not they believed the target object was the same as the object presented just prior to the last probe. N-back probes were presented for 500 ms with an ISI that was jittered between 400-800 ms, the last probe was followed by a 400-800 ms ISI and then a 500 ms target presentation. Participants then had up to 1,500 ms to provide their response using a Cedrus Corporation, San Pedro, CA-model RB-520 response pad.

Stimuli Presentation, Event Markers & Data Acquisition Management

Presentation of all stimuli (white noise, IAPS, TENS, N-back, visual cue), inputting of event markers and response pad reaction times and decision acquisition were sequenced, coordinated, controlled and recorded through in-house software within a LabView 8.2 environment on a 'Dell Inc. USA, PC, model-PWS670 using Windows XP Professional operating system, communication with external hardware/software was routed through National Instruments Co., Austin, TX, USB-DAQ-Hardware/Software Interface module, NI USB-6251 M-series connected via a National Instruments Co., Austin, TX, 68 pin shielded cable, model-SH68-68-EP to a

Coulbourn Instruments, Whitehall, PA, Power Module, model-LabLinc V, V15-17, that supported a Coulbourn Instruments, Whitehall, PA, Hardware Multi-Port, model-V19-22 E-Series Port to which all external hardware was connected.

Arousal & Emotion Elicitation Stimuli

IAPS is a series of pictures/photographs that have been empirically demonstrated to induce emotion within laboratory conditions. One-hundred and twelve-pictures, 44 neutral and 68 negative-fearful were selected from IAPS based on their affective valence ratings (Lang et al., 1999).

Images were randomly displayed at an approaching real-life/object scale as this has been shown to increase the affective response (Codispoti & De Casarei, 2007). Images were displayed for 3,500 ms. The first block consisted of sixty-six trials of 'Neutral IAPS image display,' the second block consisted of sixty-six trials of 'Negative-fearful IAPS image display,' and the third block consisted of sixty-six trials of 'Negative-fearful IAPS image display.' Images were at most displayed twice but not within the same block.

The nerve stimulation was delivered with an FDA approved device manufactured by Medi-Stim Inc., Wabasha, MN model-Arista SD+. The leads were connected to the participants' right foot (dorsal surface) approximately ½ inch apart. The TENS device was AC powered and delivered one 1-80 milliamp stimuli in square pulses at 30 pulses/sec. Participants received innocuous stimulation during blocks 1 & 2 and noxious stimulation in block 3. Subjects were asked to set their own level of stimulation for blocks 1 & 2 so as to be "totally painless, you should only be aware of the sensation, as if someone touched your foot with just enough pressure for

you to feel it." For Block 3 subjects were asked to set their own level of discomfort (pain) to 7 out of a scale of 1-11 where 1 is no pain at all and 11 is the worst possible. This protocol has been described previously by Phelps et al., (2004). Participants were told that they would not receive the stimulation on every trial during condition 3 and that the stimulation would be delivered randomly, thus they would not know in which trials the stimulation would be administered. Participants received a total of 14 noxious stimulations (out of 66 trials in block 3),

Prior to TENS a visual cue of 1-a green octagon before innocuous TENS in the neutral condition, 2- a yellow octagon before innocuous TENS in the negative condition and 3-a red octagon just prior to potentially receiving noxious TENS. Visual cues were presented for 1000 ms. ISI between visual cue and TENS was jittered between 1000-1400 ms. TENS was activated for 1000 ms per application. Generation of eyeblink startle EMG was elicited using an acoustic startle probe as per Blumenthal,et al., (2005), consisting of a white noise burst of the following characteristics: 95 dB, 50 ms duration and a virtually instantaneous rise time. The stimulus was generated and delivered via a Coulbourn Instruments, Whitehall, PA, model-V85-05C Audio Source Module. The Sounds were presented with external speakers placed approximately 12 inches from the participants ears. Two probes were delivered every third trial (the 1st was delivered the last 50 ms of the image display and the 2nd was delivered 4 seconds later, just prior to the presentation of the 1st WM probe).

Note: the use of three blocks/conditions in this study was designed to elicit three separate levels of arousal, thus the neutral IAPS was designed to elicit low

arousal, the negative IAPS was designed to elicit moderate arousal and the noxious TENS was designed to elicit high arousal. Conditions were not counter-balanced in the study in consideration of lasting neuroendocrine response that would have introduced confounds into neutral and less negative conditions were they to follow the shock/threat of shock condition and conjointly because of the lengthy duration (~1.25 hours) of the study (Bradley et al., 2003); Dickerson & Kemeny, 2004).

Additionally for the purpose of increasing motivation, participants were asked if they wanted to be part of a competition (all agreed). The competition was fully explained as read from an IRB approved document to each participant. The competition was in place for blocks 2 & 3 only. Thus, the neutral condition (1st condition) was described to subjects as "a kind of" practice condition in which they were to relax and get their strategy figured out." The competition was used as a method to keep the participants engaged in the task and ensure a high and comparable level of attention during this 1-1.5 hour task. First prize was $150, 2nd-$100 and 3rd-$50, all subjects expressed enthusiasm at their chances of winning the money (~1 in 11).

In the remainder of the document the following abbreviations regarding condition and task designation will be as follows:

Neutral Condition – Condition 1 (Presentation of neutral IAPS)
C1V – Condition 1 verbal task
C1S – Condition 1 spatial task
Negative Condition – Condition 2 (Presentation of fearful IAPS)
C2V – Condition 2 verbal task
C2S – Condition 2 spatial task
Nociceptive Condition – Condition 3 (Presentation of fearful IAPS & Shock/threat of shock)
C3V – Condition 3 verbal task
C3S – Condition 3 spatial task

Psychophysiological Recordings

EEG and EMG Acquisition.

Scalp electroencephalographic data was collected using tin electrodes housed within a stretchable lycra cap, (Electro-Cap International, Inc.). Data was acquired from 30 unipolar sites, labeled in accordance with the 10-20 international system (Jasper, 1958). At all sites of interest (F3 F4, T3, T4, P3, P4, parietal and temporal sites were analyzed so as to ensure topographical specificity of the Fads), impedances were maintained below 10 kΩ, signal was referenced to linked earlobes and a common ground. All channels were amplified 500 times using Neuroscan Synamps 1, linked to Neuroscan 4.3.3 acquisition/edit software on a Gateway Pentium computer running Windows XP operating system. Bandpass filters were set at .01-100 Hz with a sampling rate of 2,500 Hertz. EMG measurements for eyeblink startle reaction were collected through the bipolar VEOG channel and differentially band-passed at .01-200 Hz. Electrodes were placed above and below the skin of the right eye over the Orbicularis oculi muscle(Blumental et al., 2005).

Autonomic Acquisition.

Autonomic measures were recorded from the left hand, and the chest area about the heart using a Thought Technology (TT) Procomp Infiniti system, (encoder model # SA7500). Autonomic measures of Heart Rate (HR) and Skin Conductance (SC) were collected: HR was sampled at 2048 Hertz through a three electrode EKG (model # SA9306M), sensor placement consistent with manufacturers

recommendations. SC (model #SA9309M) was sampled at 256 Hertz, sensors were attached to the 2nd digit of the 2nd & 4th finger.

Procedures

Day One

The study entailed two visits to the lab. On the first day participants completed the Informed Consent, EHI, HSQ, the PANAS, BIS/BAS and the STAI (results of these affective trait questionnaires are to be reported in a separate data analysis) and were asked to take part in a non-invasive mouthwash procedure as the method to obtain their DNA sample. In this protocol, volunteers vigorously, orally swished approximately 10 ml of Scope mouthwash for 60 seconds, after which they carefully discharged the mouthwash solution into a 50 ml sterile collection tube. Volunteers were told not to swallow the mouthwash, as the intent was to collect cheek cells from their saliva for the subsequent DNA analysis (genotyping to be reported in a separate data analysis). Lastly, subjects were fitted with an EEG cap (cap and parameters of acquisition described above). Quik-Gel conducting gel was applied to a 2 site-montage via a blunt tipped medical syringe. Resting EEG was acquired during separate 2-minutes eyes open and 2-minutes eyes closed sessions. Participants to be included in Day Two were formed into two groups of 16 each. One group contained subjects with negative resting Fads and the other group contained those with a positive resting Fads

Day Two

Participants again reviewed and signed the same Informed Consent and a review of the contraindications associated with TENS. Participants were then fitted

with an EEG cap. Quik-Gel conducting gel was applied to all 32 sites via a blunt tipped medical syringe. The bipolar VEOG sites were used for EMG acquisition. Additionally, HR and SC sensors were attached as described above. Subjects were given task instructions explaining the N-back, the IAPS presentation, the eyeblink startle acoustic stimuli (they were simply told that they would hear random blasts of white noise and that it was only for data acquisitions purposes and did not pertain to successful completion of the task) and the nerve stimulation (TENS). Subjects were then given 7 practice trials without psychophysiologic recording. When impedances reach the specified levels, participants were asked to begin the task while all aforementioned electrophysiologic recordings were acquired (198 trials). Midway through each block subjects were asked to complete 6 visual analog scales (VAS) in regards to the following parameters: 1-anxiety, 2-pain intensity, 3-unpleasantness, 4-stress, 5-focus and 6- relaxed. At the end of Block 2 Subjects were given a short break for approximately 10 minutes to stretch and get a drink of water but remained in the EEG cap. Participants were then given a full written explanation of the noxious TENS stimulation and were asked to sign off on this explanation (all signed) and were then asked to begin the third block of the study (66 trials).

Data Processing

Self-Report

VASs were scored using a measurement reflecting the location at which the participant drew a vertical mark on a 100 mm horizontal line that was anchored by adjectives consistent with the dimensions listed above.

Psychophysiology

Autonomic; HR, and SC means were computed using Thought Technology version 3.1.5 software. Six summary statistics (Means) were computed during task engagement (6 bins (33 trials each) via segregation into 3-levels of Condition/stress and 2-levels of Task, spatial-verbal, (C1V, C1S, C2V, C2S, C3V & C3S).

EEG Signal Processing All EEG data reduction was performed using Neuroscan 4.3.3 edit/acquire software on all electrode pairs of interest (F3-F4, T3-T4, P3-P4). Data were visually inspected, artifact reduced, band stopped at 60 Hz and band passed at .01-100 Hz with a 24 dB/octave roll-off. All sweeps were segregated according to 3-levels of Condition and 2-levels of Task. Epochs were linear detrended, baseline corrected and visually inspected. Epochs contaminated with significant artifact were removed from further computations. State Fads scores were calculated using in-house software run on MacbookPro running OS X, using Matlab 7.01- The Mathworks, Natick, MA) (Appendix Z) Alpha power (μ^2 - 8-13 Hz) was calculated using the pwelch method of spectral decomposition and Fads were computed in one second bins (hamming windows, 50% overlap) averaged over each condition (6, 3-Condition x 2-Task) with the following formula:

$$\log \text{right } \alpha - \log \text{left } \alpha$$

Resting (baseline) Fads scores were calculated as above (as a continuous variable), means were computed over the combined (appended) 2-minute eyes-closed and 2-minute eyes-open baseline period. A resting Fads was computed for Day 1 and again on Day 2. Fad-scores used as between subjects factors in subsequent ANOVA computations were treated as a discrete variable, a positive score = 1 and a negative

score = 0 (subsequently referred to as 'Trait Fads'). All Fads entered in hierarchical regression analyses remained as continuous variables.

EMG Signal Processing—Eyeblink Startle

All EMG data reduction was performed using Neuroscan 4.3.3 edit/acquire software on signals obtained from the bipolar VEOG channel, sampled at 2,500 Hz. Data was visually inspected, artifact reduced, band stopped at 60 Hz and band passed at .01-200 Hz with a 24 dB/octave roll-off. All sweeps were segregated according to 3-levels of Condition and 2-levels of Task. Epochs were linear detrended, baseline corrected and visually inspected. Epochs contaminated with significant artifact were removed from further computations. Orbicularis oculi, EMG in response to acoustic startle probes was reduced to eyeblink reflex magnitudes using the following procedure. Eyeblink reflexes were excluded from further analysis if they contain excessive noise during a 50 ms pre-startle baseline period (e.g., blinks with unusually high amounts of integrated EMG during baseline) or because the onset of the integrated EMG eyeblink reflex began less than 20 ms following the probe. Eyeblink reflex magnitudes were calculated by subtracting the amount of integrated EMG at reflex onset (acoustic startle probe onset) from the peak amplitude (maximum amount of integrated EMG between 20-120 ms following probe onset). Trials with no perceptible eyeblink reflex were assigned a magnitude of zero and included in the analysis. A threshold of at least three good blinks per participant, per condition, per probe time (both probes of an individual trial must be artifact free for that trial to be included) was required for inclusion. Absolute eyeblink startle magnitudes as

calculated above were used as an arousal/valence manipulation check. Eyeblink startle computations were performed using in-house Matlab software.

The eye-blink startle difference score used in this study was designed to be a quantitative measure to operationally define automatic emotion regulation, JJB Allen (personal communication, February 6, 2008). The difference score was computed using the startle magnitude derived from the second white noise burst and subtracting that from the startle magnitude derived from the initial (per trial) white noise burst. We hypothesized that during elevated levels of stress (such as experienced in Condition 3) that the initial white noise burst would still elicit an enhanced eye-blink startle reflex magnitude but that the attenuation of the second white noise burst (4 seconds later) would be related to the subjects (individual and phasic) automatic/unconscious emotion regulatory capabilities. The more attenuated the second startle magnitude the greater the difference score (and the better the phasic emotion-regulation).

Behavioral--Reaction Time & Accuracy Scores (% Correct)

Reaction Time (RT) scores (continuous variable measured in milliseconds) were calculated per trial as: time elapsed from onset of target probe to execution of response button push (no response trials were not included). RT means were computed for 6 bins (33 trials each) according to 3-levels of Condition and 2-levels of Task. Accuracy Scores (discrete variable measured as correct or incorrect) were defined as match (probe = target) or non-match (probe ≠ target), correct or incorrect (no response = incorrect) and then summed and segregated into 6 bins (33 trials each) according to 3-levels of Condition and 2-levels of Task.

Statistical Analysis

Self-Report – VAS

VAS scores for all 6 dimensions (Unpleasantness, Anxiety, Pain, Stress, Relaxed & focused) were subjected to a 2 x 4 mixed design ANOVA with Trait Fads as grouping variable and a baseline (pre-task condition), along with a condition 1, condition 2 and condition 3 measures as the within subjects measure.

Psychophysiology Measures

Arousal manipulation variables (SC, HR and Eyeblink Startle Magnitudes were subjected to separate mixed-design 2 x 3 x 2 (Group x Condition level x Task type) ANOVAs with condition and task as the within subjects factors and group as the between subjects factor. Because of excessive eyeblink startle amplitudes in condition one (lack of habituation), an additional mixed-design 2 x 2 x 2 ANOVA was run w/o the 1st condition (C2V, C2S, C3V & C3S).

Eyeblink Startle Difference Scores were subjected to the 2 x 3 x 2 (Group x Condition level x Task type).ANOVA with condition as the within subjects factors and Trait Fads as the between subjects factor.

State Fads (all continuous variable Fads scores) scores were subjected to the 2 x 3 x 2 mixed-design ANOVA.

To assess the stability of resting Fads the measure was taken again on Day 2 and subjected to a t-test comparing Day 1 with Day 2 resting Fads.

Behavioral

Reaction Time (RT) and Accuracy scores (% Correct) indexing task performance were entered into two separate 2 x 3 x 2 mixed design ANOVAs: (Group x Condition level x Task type).

Hierarchical Regressions

Each of 6 variables, Performance (RT & % Correct) and Eyeblink Startle EMG amplitudes and Difference scores, HR and SC were subjected to a series of 6 (C1V, C1S, C2V, C2S, C3V & C3S) Hierarchical Regression Analyses with independent variables (1) Resting-Fads-Day 1, (2) State-Fads x Condition

State measures of parietal (P3, P4) and temporal (T3, T4) asymmetry were subjected to a hierarchical regression analysis for C3V-condition three verbal (highest level of anxious arousal) no significant results were noted.

All post-hoc comparisons were made using Tukey's HSD with a $p \leq .05$. If violations of Mauchly's test of Sphericity were observed, the Huynh-Feldt correction was applied.

Chapter IV: Results

Self Report Arousal manipulation.

The VAS analysis for unpleasantness revealed a main effect of condition, $F(3,78) = 32.031$, $p < .001$. Additionally, there was a main effect of condition for anxiety, $F(3,78) = 6.342$, $p = .001$. Post-hoc analysis revealed higher self-reported unpleasantness (PC1, M= 81.32, SE= 4.82, C1, M= 88.46, SE= 2.55, C2, M= 52.82, SE= 5.52, C3, M= 39.57, SE= 4.48) and anxiety (PC1, M= 70.32, SE= 4.26, C1, M= 73.11, SE= 3.40, C2, M= 60.25, SE= 4.75, C3, M= 55.50, SE= 4.90) during negative and nociceptive conditions compared to baseline (PC1) and neutral conditions (C1), C2 & C3 were not differentiated. There were no significant between-subject effects.

Psychophysiological measurements of arousal yielded non-significant results for HR, but there was a main effect of SC, $F(2,60) = 19.251$, $p < .001$. Further, SC (C1, M= 2.81, SE= .26, C2, M= 3.08, SE= .32, C3, M= 3.93, SE= .37) was higher in the nociceptive condition as compared to both the neutral and negative conditions, which were undifferentiated. Also, there was a condition x task interaction for absolute EBS, $F(1,28)=5.04$, $p=.033$. Post-hoc analysis revealed that absolute EBS was higher in C3V compared to all other conditions (C3V, M=221.10, SE=42.40, C3S, M=184.00, SE=41.38, C2V, M=194.94, SE=45.15, C2S, M=185.54, SE=42.39) while no other significant differences were found.

Emotional Regulation.

No significant observations were made with respect to EBS difference score or state Fads. T-test revealed Resting Fads on Day 1 were significantly higher than on Day 2 (Day 1; M = .02, SE= .03 & Day 2; M = -.11, SE= .025).

Behavioral.

For number correct and for RT there was a main effect due to condition, $F(2,60) = 6.609$, $p = .013$, $F(2,60)=39.363$, respectively. Post-hoc analysis revealed less correct (C1, M=2587.72, SE= 83.49, C2, M= 2195.70, SE= 73.11, C3, M= 2114.44, SE= 64.60)and slower RT (C1, M=30.59, SE= 0.76, C2, M= 32.28, SE= 0.18, C3, M= 32.03, SE= 0.23) in the neutral condition (non-competitive) as compared to the negative and nociceptive conditions, which were not differentiated

Hierarchical regressions.

Summaries of the hierarchical regression analysis of task performance and emotion regulation measures are provided in table 1. After controlling for trait FADS, state FADS was a significant predictor of both EBS difference score ($\Delta R2 = .215$, $p=.020$) and number correct ($\Delta R2 = .161$, $p=.031$) during the C3V condition. While trait FADS was a predictor of RT in all neutral and negative conditions, it was no longer predictive during the nociceptive condition. However, after controlling for trait FADS, state FADS was a significant predictor of RT during C3V ($\Delta R2 = .154$, $p=.071$). No other relationships were found to be significant. State measures of parietal and temporal asymmetry during the highest level of anxious arousal, condition three verbal (C3V) revealed no significant relationships.

Table 1: Summary of Hierarchical Regression Results

Measure		Standardized Beta Coefficients						
Verbal Nocioceptive	Model	Trait Fads	State Fads	R^2	Change in R^2	df	F Change	P
Number Correct	1	-.004		.000	.000	1/28	0.000	> .05
	2	.006	**.401**	.161	.161	1/27	5.173	.031
EBS Difference	1	-.147		.022	.022	1/26	0.574	> .05
	2	-.135	**.440**	.215	.193	1/25	6.150	.020
Reaction Time Conditions								
Verbal Neutral	1	**.463**		.214	.214	1/28	7.634	.010
	2	.462	-.018	.215	.000	1/27	0.011	> .05
Spatial Neutral	1	**.361**		.130	.130	1/28	4.189	.050
	2	.355	**-.373**	.269	.139	1/27	5.127	.032
Verbal Negative	1	**.429**		.184	.184	1/28	6.315	.018
	2	.404	-.243	.242	.058	1/27	2.083	> .05
Spatial Negative	1	**.409**		.167	.167	1/28	5.618	.025
	2	.394	-.133	.185	.018	1/27	0.582	> .05
Verbal Nocioceptive	1	.207		.043	.043	1/28	1.253	> .05
	2	.198	**-.333**	.154	.111	1/27	3.541	.071
Spatial Nocioceptive	1	.286		.082	.082	1/28	2.495	> .05
	2	.238	-.280	.158	.076	1/27	2.437	> .05

Note: Measurement of anxious arousal were highest during the Verbal Nocioceptive condition (shaded gray)

Table 1

Summary of the hierarchical regression results. The shaded areas represent the Verbal Nociceptive condition, eliciting the most anxious arousal as noted by the manipulation check. Notably, trait FADs was not significantly associated with the behavioral measures, number correct and reaction time, or emotion regulation measured via EBS difference score. Further, the unique variance accounted for by state FADs did significantly predict any of the three dependent measures. Specifically, higher state FADs were associated with more correct responses, faster reaction times, and increased emotion regulation.

Chapter V: Discussion

Over the span of thirty years many studies have demonstrated the association of frontal asymmetry with emotion regulatory processes (Allen & Kline, 200004; Coan & Allen, 2003; 2004; Davidson et al., 2004). Although this study adds to that body of work, it emphasizes the phasic, as contrasted to the predispositional nature, of the metric (Coan & Allen, 2006). In the major findings of this study during the highest levels of anxious arousal (shock/threat of shock) only state measures of Fads predicted emotion regulation and behavioral performance outcomes. Predispositional measures of Fads were unable to account for significant levels of explained variance during high stress. Conversely and in accord with predictions, during highest arousal (shock/threat of shock), those with more positive state measures of Fads showed significant attenuation of eyeblink startle amplitudes, faster reaction times and increased accuracy (% correct) while performing a 2-back verbal task.

Arousal Manipulation Check

In laboratory research shock/threat of shock has been set apart as a rather specific generator of anxious arousal (Greenwald et al., 1998; Phelps et al., 2004). The eyeblink startle reflex has been shown to be a reliable indicator of anxious arousal and as such is fully characterized as an index of negative valence (Bradley et al., 1999; 2006; Cuthbert et al., 1996; Lang et al., 1997). Increases in skin conductance indicate activation of the sympathetic branch of the autonomic nervous system, known to play the central role in general arousal (Andreassi, 2000; Critchley, 2005). Corroborations of subjective experience as recorded through measures such as

VAS add credence to psychophysiologic measures of affective state (Bijur et al., 2001). During the shock/threat of shock condition of the verbal task the participants were in their highest state of anxious arousal as indexed via SC, absolute EbS amplitudes and VAS measures of anxiety. Although HR differences did not reach significance, future data analyses utilizing heart rate variability (HRV) computations could reveal relevant spectral differences in the HR signal.

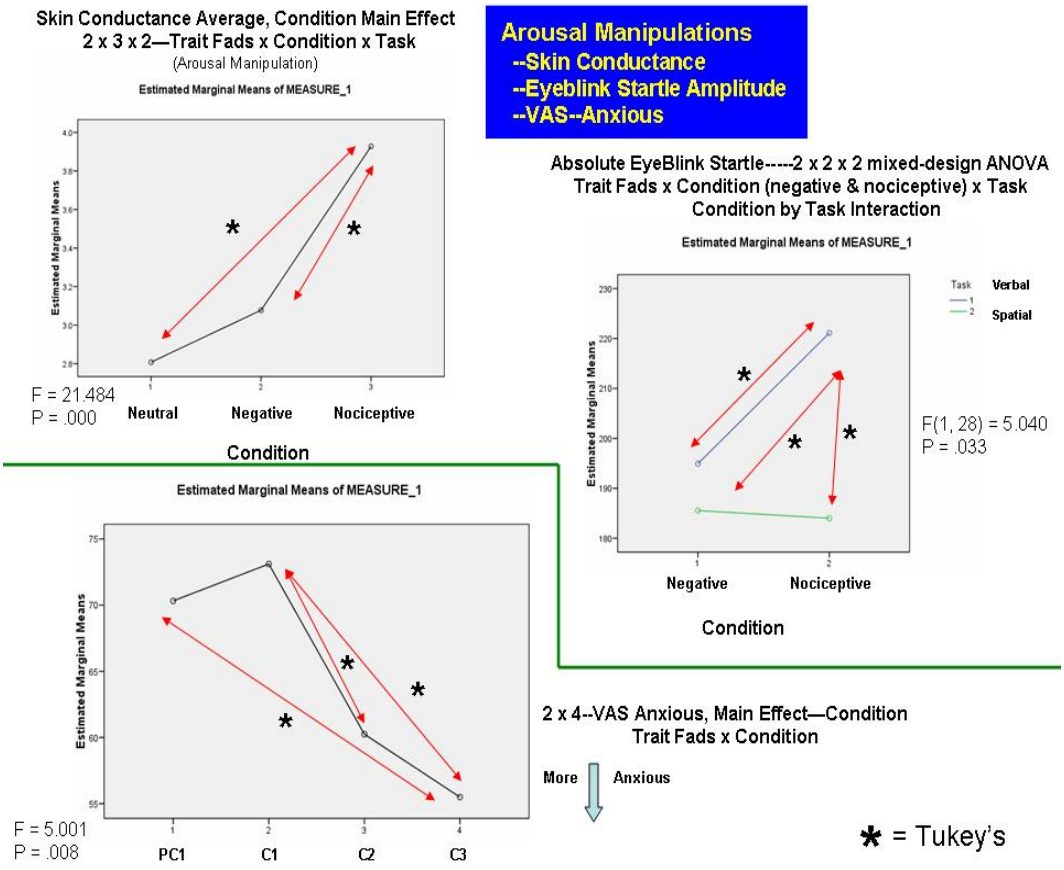

Figure 2

Arousal manipulation. The skin conductance analysis revealed increased arousal during the nociceptive condition compared to both the neutral and negative conditions. For the verbal task, EBS amplitude increased from negative to the neutral condition, also indicating increased anxious arousal. Finally, subjects reported that they were most anxious during the nociceptive condition (lower scores indicate increased reported arousal). *p<.05, **p<.01.

Expectations

Based on the extant literature (Allen & Kline, 2004; Coan & Allen, 2003; 2004; Davidson, 2004), involving trait measures of Fads, differences were expected in the ANOVAs that pertained directly to emotion regulation, i.e., EbSΔ (an index of emotion regulation). Counter-intuitively, dispositional Fads predicted neither EbSΔ nor performance outcomes. Further, using more sensitive analyses (hierarchical regression), trait Fads (now as a continuous variable) was still unable to predict emotion regulation or performance under the highest stress condition (precisely where we expected differences). However, with the addition of state Fads to the model, significant increases in predictive power were achieved. Remarkably during the state characterized as having the highest level of anxious arousal (C3V), only state (phasic) Fads was able to account for significant explained variance. And, it did so concurrently for emotion regulation (EbSΔ) and both of the acquired performance outcomes (faster RT's & increased accuracy [%correct]). The obtained results for state and trait Fads during heightened challenge, C3V (precisely where it was predicted), clearly support the 'capability model.'

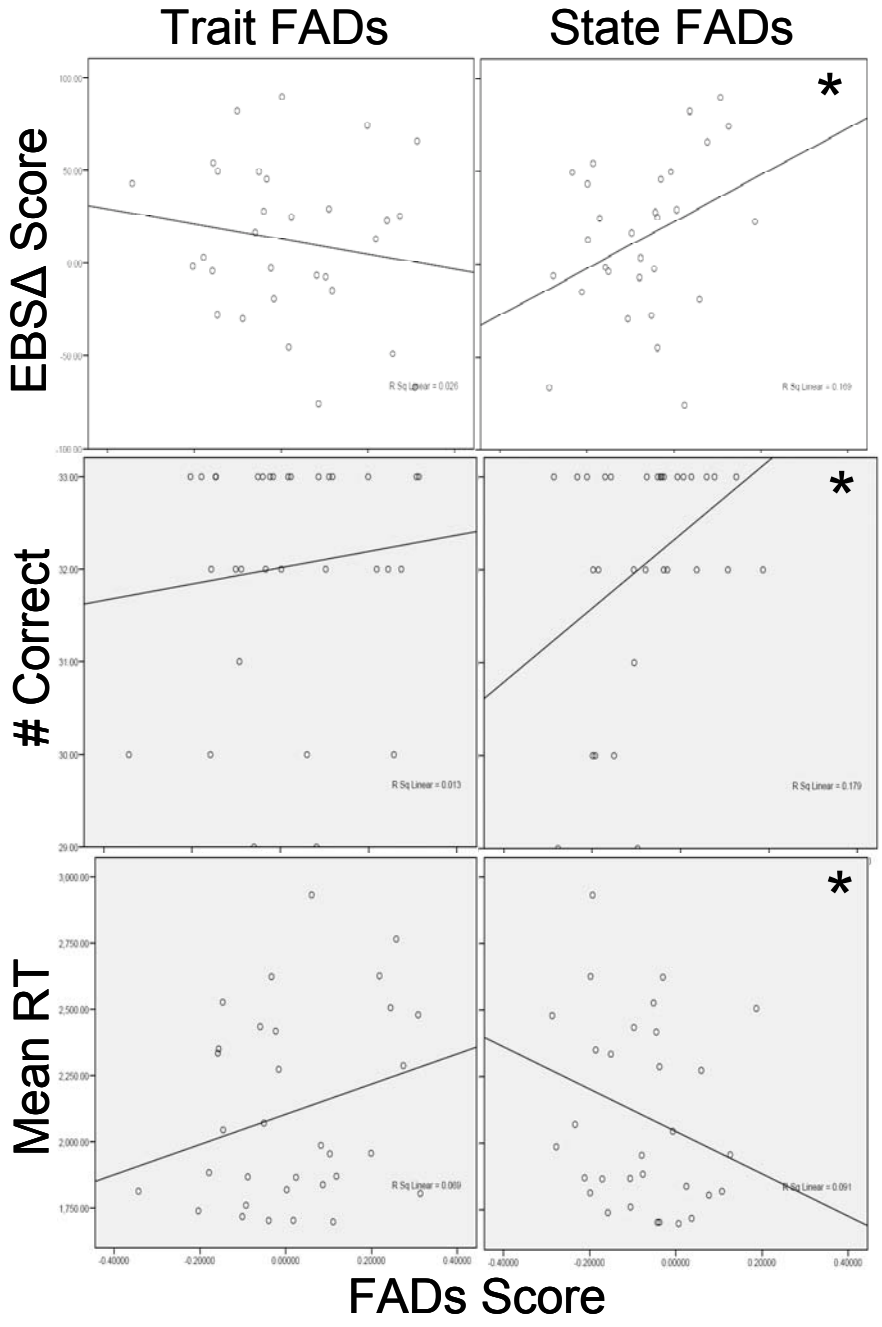

Figure 3

FADs regressions. During the most anxious arousal condition, no significant relationships were present for trait FADs and the dependent measures. However higher state FADs scores were associated with more correct responses, decreased reaction times, and improved emotion regulation. EbSΔ, *p<.05 (p-values derived from hierarchical regressions).

Trait vs. State Fads

Scientific investigation involving state measures of Fads is not new, however there is only one study, to date, we are aware of highlighting the ability of phasic Fads to explain more variance in models that examine emotion and its regulation (Coan et al., 2006; Coan & Allen, 2003; Davidson, 2004; Hagemann et al., 2002; 2005). In relevant studies using features of approach and anger behavior such as self-relevance (Harmon-Jones et al., 2006) and interactions of condition (less hungry vs. more hungry) and stimuli (appetitive vs. non-appetitive) (Gable & Harmon-Jones, 2008), Harmon-Jones et al 2005 & 2008 demonstrated that the Fads may be modulated by situational influences. A substantial number of studies (Coan & Allen, 2003) have provided examples of the circumstantial character of the metric. The current study provides additional exemplars of the situational nature of Fads and highlights the need for an operational definition of 'baseline' Fads. On Day 1 or screening day subjects predispositional frontal asymmetry measures were acquired and subsequently two cohorts were entered into Day 2 testing, sixteen positively and sixteen negatively scored-participants performed the protocol on Day 2. On Day 2, prior to testing, resting/predispositional measures of Fads were again acquired. Means were subjected to a paired t-test, with significant results ($p = .003$). Upon examination of individual means and in contrast to the resting Fads obtained on Day 1, it was noted that 28 of 32 scores were computed as negative (compared to 16 & 16 on Day 1) during the resting/baseline phase of Day 2. Participants' knowledge of the forthcoming shock is believed to account for the resultant decrease in the Fads.

Further on Day 2, the 2 x 3 x 2 ANOVA (Group x Condition x Task) of state Fads revealed no difference between positive vs. negative Fads carriers. Together these results and the predictive power of state Fads during the highest level of arousal (C3V) reinforce the notion that all measures of Fads may be "confounded" with influences of a state/situational nature. If in fact Fads has a phasic nature, what does that say about its trait measure? One inference it surely makes is, if researchers are going to continue using the metric as is, the field becomes faced with the not-so-easy task of establishing an agreed upon and objective measure of exactly what that baseline is. Raichle's (Gusnard & Raichle, 2002) noteworthy research in establishing an fMRI baseline perhaps reveals both the difficulty and rewards of such an undertaking. However, how to follow Raichle's lead in the field of EEG is an empirical question not as of yet answered (asked?). Parsimony dictates first and foremost that we accept the more fundamental explanation regarding any set of results. Thus, the idea that state Fads may explain trait scores (more anxious = more negative to simple laboratory visit) but not vice versa, provides a somewhat compelling reason to do away with trait fads as it is currently measured (but not the pursuit of a Fads-related, trait-like metric).

Frontal Influence in Emotion and its Lateralization

A possible reason for the positive associations between state-frontal activation and behavioral performance is based on management of amygdalar activation and consequent arousal of cortical processes (increased signal to noise) More specifically the fronto-parietal attentional network (Adcocok et al., 2000; Hedden & Gabrieli,

200; Pessoa, 2008; Yamasaki et al., 2001) is likely refined and adaptive in its state, thus enabling superior reactivity (RT & accuracy).

The neuroanatomical basis of fronto-amygdalar connectivity along with both regions' executive influence over autonomic control centers is well established (Critchley, 2005; Davidson, 2004; Ghashghaei et al., 2007; LeDoux, 2002; 2002b; Pessoa, 2008; Quirk & Beer, 2006; Rolls, 2005; Vogt, 2005). Notable studies have demonstrated inverse activations between PFC and amygdala (Kim et al., 2003; Ochsner et al., 2002; Pare et al., 2004; Quirk et al., 2003; Urry et al., 2006). The PFC is implicated in up and down-regulating both amygdalar impact and of directly influencing control centers of autonomic processing. Additionally, considerable evidence has amassed supporting functional lateralization in regards to affective processing (Allen & Kline, 2004; Bechara et al., 2000; Craig, 2004; 2005; Critchley, 2005; Critchley et al., 2005; Davidson, 2004; Murphy et al., 2003; Noesselt et al., 2005; Ochsner et al., 2002; Phan et al., 2004; Pizzagalli et al., 2005; Vogt, 2005). To very briefly sketch this literature: left frontal activations are dominated by approach behaviors and positive valence, while right frontal activation is associated with withdrawal behaviors, negative valence and arousal. As noted before, important new work, Craig, (2005), provides a solid foundation for this lateralization, which the author roots in the hierarchical neuroanatomy and paired opponent processing of the autonomic nervous system. The core of Craig's 2005 model reflects principles of organismic energy management in which energy enrichment is associated with the left forebrain and energy expenditure is associated with the right forebrain. A prototypical example of this comes from two separate studies from the same lab

showing that dominant efferent innervation of cardiac parasympathetic electrophysiology derives from left hemisphere control centers while the opposite holds for sympathetic efferents (Craig, 2005; Wittling et al., 1998; 1998b). These noteworthy results further solidify the notions of lateralization of frontal function, in regards to emotion and cognition interactions, provided by thirty years of distinguished EEG/neuroimaging study by Davidson and colleagues.

Integration of Emotion and Cognition vs. Dissociation

The number of studies demonstrating the positive effects of emotion on cognition has grown considerably in the past fifteen years. Moderate levels of emotion have been implicated in enhanced learning, memory, attention, adaptive reasoning and even the sharpening (multiplicative gain of relevant vs. non-relevant features) of sensory processing (Bechara et al., 1997; Egner & Hirsch, 2005; Glascher et al., 2007; LeDoux, 2002b; Pessoa, 2008; Phelps & LeDoux, 2005; Sharot & Phelps, 2004). Additionally, studies of high anxious arousal and emotional distracters have shown emotion's negative effect on the same (enhanced) cognitive processes mentioned above (Chen et al., 2005; Lavric et al., 2003; Phelps et al., 2004; Shackman et al., 2006). Recent studies have begun to elucidate cognition's effect on emotion (Blair et al., 2007; Gray et al., 2002; Pessoa, 2008; Pessoa et al., 2006; Salomons et al., 2004). In the Blair et al., (2008) study, emotional and cognitive regions were monitored (fMRI) while subjects passively viewed emotional stimuli, these activations were contrasted to the presentation of equivalent emotional stimuli while subjects were engaged in cognitive challenge. Analysis revealed significant inverse activation patterns in predominately cognitive vs. predominately affective

areas between the two conditions. Interestingly, within the same study emotion's effect on cognition and cognition's effect on emotion were demonstrated. Rooted in its performance results, the current study provides another example of the complex interactions of emotion and cognition (Coan et al., 2006; Gray , 2004; Gray et al., 2002; Ochsner & Gross, 2005; Pessoa, 2008; Rolls, 2005). When examined through the lens of individual difference (albeit situational) as indexed by phasic Fads, only those with increased state-Fads during the highest level of anxious arousal were 'capable' of down-regulating negatively valenced affect (via EbSΔ) while concurrently increasing performance (higher %Correct & faster RT's). Thus, we may in part define successful integration of emotion and cognition as, the degree to which one can match their emotion regulatory 'capabilities' (as measured via state-Fads) to the environmental demands of the situation.

Do We Need a New Metric of Frontal Asymmetry?

One of the limitations of this study and of the current literature in terms of understanding the neural correlates of Fads is: at this point in time and in regards to the laboratory activities participants have engaged in, the opportunity to withdraw on a trial by trial basis has not been offered and therefore constrains the inferences drawn regarding withdrawal behavior as psychophysiologic measures surrounding the actual decision/execution of withdrawal have not been acquired. This idea in conjunction with continuing evidence for the capability model and the results of the current study (state Fads scores during C3V did not reach positive values they were only 'less negative') may in fact force us to look at the idea that the neural correlates of Fads (and this would be reflected in the scores) may be better thought of as two orthogonal

axes, much like Berntson & Cacioppo (Bernston et al., 1991; 1993) have described for sympathetic and parasympathetic activation of the ANS.

Perhaps the noted inconsistencies in trait measures of Fads, may in part be resolved by devising a state-based metric. The significant results tying biological markers of anxious temperament, such as, CRH, cortisol, antibody response and EbS magnitudes to measures of trait Fads (Jackson et al., 2003; Kalin et al., 1998; 2000; Rosenkranz et al., 2003) may in fact be enhanced by the utilization of state measures. This state-based metric must account for Fads across a wide range of situations. Scores need be acquired between different categories (happiness, fear), and when approach and withdrawal behaviors are both adaptive and maladaptive. Does one approach or withdraw from the saber-tooth tiger, is a situational question. If I am toting the appropriate weapon, I approach and if not I withdraw. Interesting paradigms arise from the athletic phenomenon known as "choking." Choking begs the question, what are Fads (its neural correlates) doing when an experienced performer does well vs. 'chokes.' Too often approach is written of as "positive" and withdrawal as "negative," although an obvious oversimplification, these generalizations persist. Similarly as Craig's 2007, ANS-based model of forebrain asymmetry is tested it will be temping to look at left-parasymapthetic activation as positive and right-sympathetic arousal as negative. However, the wealth of studies (Hillman et al., 2008)[128] demonstrating the beneficial attributes of exercise (sympathetic activation), points out the flaws in such logic.

There is a conundrum inherent in the development of any state based metric. In order for research to assist in the assessment and /or remediation of one's emotion-

cognition integrative capabilities an index that need be measured less than in "every possible state" must be devised. Building on suggestions made by Coan et al, (2006), a number of ideas are offered: 1-formulate a metric analogous in concept to Heart Rate Variability (HRV) in which measures of state-Fads responses to approach stimuli and withdrawal stimuli are conjointly utilized to compute this new metric (a variability score, for ex.-a person's Fads in a highly aversive situation is subtracted from their Fads in a highly appetitive situation), 2-Use signal processing tools with better resolution than one-second Fourier Transforms, for ex.- narrow a bandpass filter so as to allow only 8-13 Hz signal (or inversely a gamma (30-80 Hz bandpass), then compute the difference score from peak to peak measurements of those signals as derived from frontal homologous electrodes, then plot the difference score as a continuous line plot with event markers inserted appropriately from the experimental paradigm so as to better visualize the dynamics of Fads, 3-include actual instances on a trial by trial basis in which participants physically withdraw from aversive stimuli (such as cold pressor) and then approach a stimuli (such as plunging their cold hand into warm water-the same hot and cold stimuli could actually be used to assess both approach and withdrawal behavior), 4-Use other high resolution signal processing tools such as phase synchrony (Sejnowski, 2006; Varela et al., 2001) to examine the networking characteristics of gamma phase locking during concurrent changes in state Fads, 5- use Wavelet based techniques to determine with better time resolution the pattern of changes in activation (spectral power) between frontal left and right homologues in response to event marked stimuli(Handy, 2005), 6-Simultaneous EEG and fMRI (Babiloni et al., 2004; Mizuhara et al., 2005; Oakes et al., 2004) and/or

source localization techniques(Michel, 2004) in which state measures of Fads and their generators are entered into functional connectivity analyses. Perhaps, in the tradition of HRV measures(porges, 2007), some well orchestrated combination of these techniques (and/or others) will derive a single metric (Fads-related) reflecting one's capabilities in regards to the integration of emotion and cognition (within the approach-withdrawal dimension).

Many distinguished researchers (Buzsaki & Draguhn, 2004; Davidson & van Reekum, 2005; Gray et al., 2002; LeDoux, 2002b; Pessoa, 2008; Pribram, 2003; Rolls, 2005; Sejnowski & Paulsen, 2006; Sporns et al., 2007; Varela et al., 2001) are calling for higher order levels of analysis that emphasize the integrative, dynamic and interconnected aspects of what Ledoux, (2002b) calls the big three of brain function, cognition, emotion and motivation. Cacioppo, (2004), asks the question, "…whether the various correlates of EEG asymmetry are themselves sufficiently correlated that they likely result from a unitary underlying faculty or mechanism?" After which he issues a caution worth listening to, "literature has also revealed that the psychological interpretation of an ERP measure may differ across paradigms---a finding that should serve as a cautionary note to those who wish to interpret EEG asymmetry measures as necessarily reflecting the same substrates, predispositions, or information processing operations across different paradigms or methods of measuring frontal asymmetries (cf. Hagemann et al., 1998, Reid et al., 1998)." The participants of this study who were able to increase state-fads during the highest level of anxious arousal, attenuated their anxiety (EbSΔ**)**, maintained an adaptive level of general arousal (Yamada et al., 2006, show increased SC in service of successful emotion regulation), stayed focused

(reward from the competition) and performed more accurately (%Correct) while executing their decision/movement more quickly (faster RTs). This is a complex, situational and balancing act kind of 'approach'— not the either / or kind.

Appendix I: IRB Documents

UNIVERSITY OF MARYLAND
INSTITUTIONAL REVIEW BOARD

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College Park, Maryland 20742-5125
301.405.4212 TEL 301.314.1475 FAX
irb@deans.umd.edu
www.umresearch.umd.edu/IRB

November 26, 2007

MEMORANDUM

Application Approval Notification

To:	Dr. Bradley Hatfield Ronald Neil Goodman Department of Kinesiology
From:	Roslyn Edson, M.S., CIP RE IRB Manager University of Maryland, College Park
Re:	**IRB Application Number: # 07-0187 (PAS 1720)** **Project Title:** "Performance Under Pressure: Examination of Relevant Neurobiological and Genetic Influence"
Approval Date of Addendum:	**November 8, 2007**
Expiration Date of IRB Project Approval:	**May 24, 2008**
Application Type:	***Addendum / Modification;*** Approval of request, submitted to the IRB office on September 20, 2007 to (1) offer an optional competition for accuracy and quickness during the working memory task, (2) offer three cash prizes: 1ST prize - $150, 2ND prize - $100, and 3RD prize - $50, and (3) use the following documents to reflect these changes: informed consent form, human subjects review protocol, a telephone script, and a recruitment flyer.
Type of Review of Addendum:	Full Board / Degree of Risk: Greater than minimal
Type of Research:	Non-Exempt

The University of Maryland, College Park Institutional Review Board (IRB) approved your IRB application. The research was approved in accordance with 45 CFR 46, the Federal Policy for the Protection of Human Subjects, and the University's IRB policies and procedures. Please reference the above-cited IRB application number in any future communications with our office regarding this research.

Recruitment/Consent: For research requiring written informed consent, the IRB-approved and stamped informed consent document is enclosed. The IRB approval expiration date has been stamped on the informed consent document. Please keep copies of the consent forms used for this research for three years after the completion of the research.

Procedures Used*:** from the International Affective Picture System (IAPS) that are designed to elicit emotional responses, picture contents will range from neutral-picture of a telephone, to fearful-guns pointing at people, snarling animals and scenes depicting other fearful events such as an attacker holding a knife to a victim's flesh with blood spilling. After the viewing of the picture you will be shown a series of words or objects and then will be shown a single word or object and will be asked to hit a response button if that word or object was the same as the one viewed 2 pictures back in the series (called an N-back In phase two you will perform the same task just prior to the administration of a moderately painful electric stimulation. The TENS unit described above when turned up fully (we are not going to do this- as you will set your own level) causes uncomfortable-painful sensations but typically never reaches "unbearable" levels. The equipment is FDA approved. You will be asked to review and sign, an instruction sheet that asks you to select your own level of stimulation to equal a pain level equivalent to a 7 out of 11 on a scale with, 1 being no pain at all and 11 being unbearable, this is consistent with what has been done in previous studies at major U.S. research institutions The stimulation will last from two-five seconds and at any time, at your request, you may be immediately excused from any further stimulation. A reference list of other studies of this nature from major US research institutions will be available upon request. *We want to emphasize that the competition is completely optional and voluntary and that you may choose to withdraw from the competition at any time and that withdrawal from the competition will not affect your participation in the rest of the study and you will still receive your compensation. There is an approximate 1 in 10 to 1 in 12 chance of you winning money in this competition. If you win, you will be notified by both phone and email. Lastly, in the final condition in which the moderately painful TENS stimulation will be delivered there are 60-66 trials* ***however*, you will receive the TENS simulation only between 8-18 times (how ever, this is random and you will not know on which trials the stimulation will be delivered). This does not differ either if you are in the competition, or you choose not to compete.*

Confidentiality: All information collected in the study is confidential; your name will not be identified at any time except for the Informed Consent and the form you sign to set the level of TENS stimulation. The data you provide will be grouped with the data of others for the purpose of reporting and presentation so that your individual data will not be identified. All data will be kept at the University of MD, in the HLHP Building Room 2303A in a locked cabinet to which only research team-members have access. The list that links your name to your ID number will be kept in a locked box in Dr. Hatfield's office, to which only he or his designee have access. All data will be destroyed 10 years after its analysis, in 2017.

Risks: You understand that the administration of moderately painful electric stimulation (TENS) will cause you discomfort to moderate pain and you may experience a temporary (a few hours) reddening of the skin around the area of the electrode placement. However, TENS is used safely and frequently in clinical and home settings across the USA.

Continuing Review: If you intend to continue to collect data from human subjects or to analyze private, identifiable data collected from human subjects, after the expiration date for this approval (indicated above), you must submit a renewal application to the IRB Office at least 30 days before the approval expiration date.

Modifications: Any changes to the approved protocol must be approved by the IRB before the change is implemented, except when a change is necessary to eliminate apparent immediate hazards to the subjects. If you would like to modify the approved protocol, please submit an addendum request to the IRB Office. The instructions for submitting a request are posted on the IRB web site at:
http://www.umresearch.umd.edu/IRB/irb_Addendum%20Protocol.htm.

Unanticipated Problems Involving Risks: You must promptly report any unanticipated problems involving risks to subjects or others to the IRB Manager at 301-405-0678 or
redson@umresearch.umd.edu.
Student Researchers: Unless otherwise requested, this IRB approval document was sent to the Principal Investigator (PI). The PI should pass on the approval document or a copy to the student researchers. This IRB approval document may be a requirement for student researchers applying for graduation. The IRB may not be able to provide copies of the approval documents if several years have passed since the date of the original approval.

Additional Information: Please contact the IRB Office at 301-405-4212 if you have any IRB-related questions or concerns.

Risks:

Situations and or Conditions when Subjects Should Not Participate:

1-TENS should not be used in patients with pacemakers or defibrillators as it could disrupt their function
2-TENS should not be used during pregnancy as it may induce premature labor
3- TENS should not be applied over the carotid sinus (the neck/throat) as it may cause acute lowering of blood pressure
4- TENS should not be applied anywhere over the neck as it may cause laryngospasm (contraction of the muscles of the voice box causing difficult breathing in but typically not effecting breathing out, usually lasts 30-60 seconds.
5- TENS should not be used if one might have nerve or skin damage in the area of electrode placement as burns could result
6- TENS should not be used on anyone with a history of Seizure/Epilepsy
7-TENS should not be used on anyone with Asthma
8- TENS should not be used on anyone with Psychiatric illness
9-TENS electrodes should never be placed on the chest or head
You will select your own level of discomfort by you deciding the setting on the TENS unit but as mentioned before we ask that you approximate a 7 out of a 11 on the scale that will be described to you on the instruction sheet you will be required to sign . Additionally, you understand that, as a result of wearing the EEG cap to measure brain electrical activity, you may experience slight sensations and irritation of the skin as the scalp is lightly rubbed at the electrode sites. There is a risk that your skin may be broken during EEG electrode preparation, however this is rare in our lab. Also note that a small number of people may be allergic to the conducting gel and or adhesive used on the throw away-single use electrodes but this is rare. Please let us know if you are experiencing irritation around electrode placement areas. There are no known risks associated with the measurement techniques used in this study to access Heart Rate, Skin Conductance, Muscle Tension (acoustic startle probe) or Cortisol levels. Even so, there are minimal risks to you if you participate in this study. There is a risk that some people may find the IAPS pictures disturbing. There is a possible risk that some people may find the white noise causes them discomfort. Lastly, there is a risk of fatigue since you will be wearing the EEG cap and performing the working memory task over a long period of time (1 1/2 -2 hours). Again please note the 'Situations and Conditions when Subjects Should Not Participate' above. If you are a female and wish to participate you must provide a negative pregnancy test-result within one week of session two.

Benefits:

You understand that the experiment is not designed to help you personally but that the investigators hope to learn more about the mental processes involved in working memory performance in order to improve performance in others.

Initials_____Date_____

Freedom to

Withdraw: You understand that you are free to ask questions about the study or to withdraw from the study at any time, without penalty. You understand that you will have a signed copy of this consent form given to you and that the investigators will provide you with the results of the study (however, genotypic information cannot be given out).

Where Medical Care is Available: You understand that the University of Maryland does not provide any medical care or hospitalization insurance coverage for participants in this research study, nor will the University of Maryland pay any medical expenses or provide any compensation for any injury sustained as a result of participation in this research study, except as required by law.

Informed Consent: *"I am voluntarily making a decision whether or not to participate in the research study described above. My signature indicates that I have decided to participate having read the information provided above and having had all of my questions answered. I will be given a copy of this consent form to keep.*

Printed Name of Participant_____

Signature of Participant_____

*Please check this space if you wish to be entered in the competition*_____

Signature of Witness_____

Date of Signatures_____

Dr. Bradley Hatfield
Department of Kinesiology
College of Health and Human Performance
University of Maryland
College Park, MD 20742
301-405-2485
bhatfiel@umd.edu

Initials_____Date_____

June, 2007

Project Title: "Performance under Pressure: Examination of Relevant Neurobiological and Genetic Influences"

Project Director: Dr. Brad Hatfield, Dept. of Kinesiology
Student Researchers: Ron Goodman, Jeremy Rietschel, Li-Chuan Lo, Min Jung Woo, Mark Saffer & Michelle Costanzo

Human Subjects Review

Appendices

Appendix a: Informed Consent
Appendix b: Edinburgh Handedness Inventory & Coan Test
Appendix c: Health Status Questionnaire
Appendix d: Spielberger Trait Anxiety
Appendix e: PANAS
Appendix f: BIS/BAS Scales
Appendix g: Visual Analog Scales
Appendix h: Putnam et al. 1992
Appendix i: TENS Equipment Information & FDA approval & Safety Guidelines
Appendix j: List of References of Major Research Institutions using Aversive/Nociceptive Stimuli in Recent Studies
Appendix k: Instruction Sheet for Subjects to choose level of Aversive/Electric stimulation
Appendix l: International Affective Picture Series (IAPS) Information
Appendix m: Recruitment Flier & Telephone Script for Screening Participants
Appendix n: Acoustic Startle Probe Equipment Information & Safety Specifications & References from Literature for its use

University of Maryland, College Park, MD
Human Subjects Review Committee

March, 2007

Project Title: "Performance Under Pressure: Examination of Relevant Neurobiological And Genetic Influences"
Project Director: Dr. Bradley D. Hatfield, Dept. of Kinesiology, University of Maryland, College Park, MD 20742
Student Investigators: Ron Goodman, Jeremy Rietschel, Li-Chuan Lo, Min Jung Woo, Mark Saffer & Michelle Constanzo, University of Maryland

1. Abstract/Overview:

The purpose of this study is to assess the influence of emotional arousal on brain processes and cognitive performance during a working memory task. Twenty-Thirty participants, who differ in emotion regulation as determined from brain electrical activity and genetic factors, will be recruited to perform the working memory task. The task will be performed under three different conditions of emotional arousal – (1) low, (2) moderate, and (3) high. In order to manipulate arousal the participants will be presented with emotion-eliciting picture stimuli in the first two conditions (i.e., low and moderate arousal) and a combination of picture stimuli and transcutaneous electric nerve stimulation (i.e, moderate pain) in the third condition (i.e., high arousal). More specifically, the participants will view scenes selected from the International Affective Picture System (IAPS-see appendix k) and the transcutaneous electric nerve stimulation (TENS) (appendix i) will be induced by passing a small current to excite peripheral nerves (i.e., 1 to 60 milliamps). TENS is widely used in clinical settings to relieve chronic pain. (Note: Subjects will select their own level of electric stimulation to achieve an individually determined level of discomfort (i.e., moderate pain). (When used properly no tissue damage is typically reported in the literature and this procedure and equipment is within a minimal risk profile). The low-arousal condition will be elicited by the presentation of neutral scenes from the IAPS, such as a picture of a telephone, and *there will be no*

presentation of moderate electric stimulation. The moderate arousal condition will be elicited by the presentation of negative / fearful scenes from the IAPS such as a picture of a gun pointed at one and, again, *there will be no presentation of moderate electric stimulation.* Finally, high arousal will be elicited by the presentation of negative / fearful scenes from the IAPS as well as *presentation of moderate electric stimulation.* We predict that arousal will be related to working memory performance in a curvilinear manner, such that moderate arousal will facilitate performance and high arousal will degrade it. Importantly, the magnitude of decline under high arousal will be attenuated by those who can successfully regulate their emotion. As such, a central focus of this research is the role of individual differences in emotion regulation. The frontal brain region has a clearly established role in arousal regulation because of the circuitry between it and the emotion centers of the brain (i.e., limbic structures that orchestrate the "fight or flight" response). Therefore, an index of emotion regulation will be determined from frontal brain activity measured by non-invasive electroencephalographic (EEG) recordings. More specifically, a frontal activation difference score (FADS) will be computed between left and right EEG, whereby a positive score is indicative of superior emotion regulation. Thus, we expect that those participants (n=10-15) with higher FADS scores will better manage their arousal, particularly under high arousal and perform the memory task better than those with lower FADS scores (i.e., the low-FADS group). The EEG will be used to assess (1) brain activation in specific regions of interest and (2) networking between specified cortical regions. We expect to see significant changes in regional communication (EEG coherence) between affective, sensory and executive control centers of the brain in all participants. The predicted changes in the brain during these stressors are indicative of effortful attentional processing and excessive neural processes that may interfere with working memory performance, resulting in lowered accuracy, inconsistent performance and delayed learning. However, we expect the high-FADS group to exhibit greater relaxation and refined communication between different cerebral cortical regions as well as lower heart rate under the condition of high arousal, relative to the low-FADS group. Additionally, the role of individual differences in the relationship between emotional arousal and cognitive performance

will also be assessed with consideration of genetic influence. More specifically, a complementary regression analysis (i.e., beyond the planned factorial Groups x Arousal conditions ANOVA approach described above) will be applied to the memory performance scores. The genotyping employed in this study will determine allelic variants of the Catechol-O-MethylTransferase (COMT) gene and the 5-HydroxyTryptamine Transporter Linked PolymoRphism (5-HTTLPR) of the SERT gene. These two genes have a well established role in both the processing and regulation of emotion. The results of this study will help to explain how individual differences modify the manner by which psychological stress affects the quality of cognitive performance. This study will have a day one and a day two, with day two occurring two-three weeks following day one. Day one will be brief testing to determine high and low emotion regulation groups. Day two will be EEG acquisition and subjects will be challenged with the working memory task under the three arousal conditions.

Human subjects will be protected during this study using multiple methodologies:

a. Informed consent, assuring the subject's understanding of the nature of the research and the tasks, as well as the potential risks and benefits of the study, will be obtained from all subjects prior to participation on both day one and day two.
b. Research methodologies and equipment employed (EEG, Peripheral Psychophysiology, acoustic startle probe & IAPS) have been used in prior studies, without known adverse affects on subjects.
c. Research methodologies and equipment employed (TENS) have been used in prior studies, without any known lasting adverse affects on subjects (when used properly no tissue damage is reported as this methodology is used therapeutically for nerve damage victims). There will be 80 trials during the high arousal condition. Subjects will experience 2-5 seconds/trial of moderately aversive stimulation in only 16 of the 80 trials, which will be randomly delivered–this occurs only during the second phase of session two.
d. A subject's confidentiality will be protected via the absence of any links from the person's identifying information to any of the data collected –either in paper or electronic form. Only research staff involved with the study will have access to any of the data collected. Data collected will be grouped with data collected from other subjects for presentation. Only the Informed Consents and the sign-off sheet for subjects to set their own level of TENS stimulation will have names attached.

e. Subjects' dignity and right to withdraw will be respected at all phases of the research project. Subjects may ask questions at any time during the process. Subjects may withdraw at any time, without penalty.

f. All subjects with any of the following conditions will be excluded from the study:

1-Any form of heart condition
2-Current use or history of a Pacemaker or Defibrillator
3-Any abnormal skin or skin damage on lower legs
4-Any nerve damage on lower legs
5-Any history of seizures
6-Any major organ illness
7-If pregnant-and all females must provide a negative pregnancy test-result within one week of session two
8-Any history of Asthma
9-Any history of psychiatric illness, ex.-panic attacks

2. Subject Selection:

a. Sixty-eighty volunteers will be screened and twenty-thirty participants will be recruited
b. Participants selected will be students recruited from UMCP.
c. Subjects will be recruited in the 18-35 year old age group and be healthy, typical, high- functioning (no known health conditions) individuals.
d. The working memory task is useful as it allows for a motionless (pertaining to head movement) task that enables EEG recording during performance. The task is easily scored so that the relationship between brain activity (EEG) and working memory performance can be objectively determined. Only right-handed and ipsi-lateral eye-dominant subjects will be used so as to avoid hemispheric artifacts.

3. Procedures:

The purpose of the study is to examine how emotional arousal and physiologic stressors effect brain activity during performance of a working memory task and to contribute objective measures of emotion regulation (ER).The results of this research may help in the design of future therapeutic interventions to enhance human performance in many essential areas such as emergency medicine, military, law enforcement, music and athletic performance, public speaking, family and social interactions and in emotional psychopathology.

Prior to each testing session participants will be asked to refrain from consuming any alcohol on the day of testing. Additionally they will be asked to refrain from eating, brushing their teeth, or drinking caffeinated beverages or large amounts (>1 Qt.) of water/liquid for at least one hour prior to testing in order to enable valid salivary cortisol (i.e., stress hormone) samples. After arriving at the screening site participants will be informed about the requirements of the experiment and will be given an opportunity to ask questions. They will then be asked to read and sign the consent form (see Appendix a) if they are willing.

The study will consist of two sessions with the second session having two phases. The first session will last approximately 30 minutes. Subjects will complete five questionnaires (appendices b, c, d, e and f). Participants will then be asked to swirl 'Scope' mouthwash in their mouths for 30 seconds and then place the 'wash' in a small sterile tube for DNA analysis. Lastly, they will have two EEG electrodes attached to their ear lobes and two EEG scalp electrodes attached slightly above and back form their foreheads (frontal lobe). Electrode attachment will be done as described below (next paragraph), except that only four electrodes will be attached and therefore the time to attach will be about 5 minutes and the time to record only 8 minutes, removal is less than two minutes.

The second sessions will be executed two-three weeks later and will consume approximately 2 hours with about 30 minutes for cap fitting and gelling and 1 1/2 hours for data acquisition and cap removal. On arrival, subjects will review and sign another copy of the Informed Consent and fill out the 'Day Two Exclusionary Review.' When complete, participants will be fitted with a stretch-lycra Electrode International (ECI) cap that houses 64 recessed EEG sensors formed from tin. The participant's skin will be lightly abraded or rubbed with the end of a Q-tip at each sensor site to remove oil and dead epidermal tissue to establish good conductance of the EEG signal. The skin will not be broken. Using a blunt applicator attached to a syringe, an FDA-approved non-toxic conducting gel will then be applied through an opening in each of the 64 recording sensors to establish continuous contact of the gel between the skin at the recording sites and the corresponding sensors. Recording sensors will also be positioned on the skin above and below the left eye to monitor eye movements as well as on both ear lobes to serve as "non-brain" reference sites. A ground electrode site will be applied in the frontal region. The eye-channel and reference sites will be lightly abraded with a pad, rubbed with alcohol, and prepared with the conducting gel to enable continuous connection between the scalp and the sensor surface. Participants will be asked to wear headphones and at two different time intervals during the working memory task EMG measures of muscle tension will be collected from the EEG eyeblink electrodes after the delivery of short burst of innocuous white noise (99 dB, 50 ms duration with a virtually instantaneous rise time). This is known as an acoustic startle probe and is used as an index of automatic emotion regulation. The stimulus will be generated and delivered via a Coulbourn V85-05 white noise generator (appendix n). The Sounds will be presented through research grade earphones (TDH Model—49; *Telophonics).* Note the dB level is well below the 120dB harmful noise threshold and of such a short duration as to make this well within a minimal risk profile. See appendix n for white noise generator equipment specifications and safety features and the *Committee Report: Guidelines for human startle eyeblink electromyographic studies, Blumenthal et al, 2005 which contains a comprehensive reference list* of studies by major research universities that have safely employed this technology.

Additionally, three electrodes will be placed on the subject's chest near their heart in order to measure their heart rate and two small sensors will be placed on fingers of their non-dominant hand to measure skin conductance. Lastly, the TENS electrode will be administered to the skin of the subjects non-dominant foot/ankle. All recording will be done in accord with Society for Psychophysiological Research Ad

Hoc Committee Report Guidelines for Reducing the Risk of Disease Transmission as outlined by Putnam et al. (1992) (see Appendix g) and all researchers will wear approved latex gloves while working with the participants to further reduce any risk of infection. After usage all EEG caps are: a) soaked for 20 minutes in mild detergent, b) mechanically cleaned with throw away cotton swabs, c) rinsed in running, hot 120-140° F, tap water, d) soaked in full spectrum disinfectant for 20+ minutes (much longer than manufacturer's recommendations), e) and air dried for at least 24 hours prior to reuse. EEG electrodes are made of tin. Skin conductance electrodes are tin and flat surfaced, no abrasion is necessary for placement of skin conductance electrodes, the skin is lightly rubbed with rubbing alcohol and the electrodes are rubbed with alcohol after and prior to administration. Both EKG and TENS electrodes are stick-on, single use electrodes. All blunt-end needle-gel applicators are single use and disposed of in appropriate bio-hazard disposal containers. All electrical equipment is UL listed and fully grounded to eliminate any hazard of electric shock. The TENS unit is FDA approved and a brochure is enclosed (see appendix i). The TENS unit is manufactured by EMPI Inc., St. Paul, Minn. It is a conventional style unit and the model is known as 'Select' and will be purchased new. Dr. Mark Saffer (Neuroscience and Cognitive Science doctoral student), a licensed chiropractor in the state of Maryland is a member of our research team and is involved with the planning and execution of this study. Dr. Saffer has put together a safety guidelines sheet for the use of the TENS unit and all members of our research team must read and sign off on this document (see appendix i). In order to exclude any subjects with possible preexisting nerve damage researchers will comply with the procedures described in appendix i. More specifically the researcher will administer the Semmes-Weinstein test of sensory function to the dorsum of the foot to which the electrodes will be applied. This is a standardized clinical test, see appendix i, the 'Safety Guidelines for Researchers.' All subjects who do not show a normal range of sensation will be excluded from the study. Headphones used in this study will be wiped with an antiseptic alcohol pad after and prior to each use.

Upon completion of the above procedures subjects will select their level of discomfort using the (TENS) electrode and starting at the lowest setting (which is typically innocuous and used for therapeutic applications), the subject will experience electric stimulation at increasing levels till they say OK that level is appropriate to elicit a moderately painful level of stimulation. See appendix i for equipment information and see appendix j for list of studies performed by major research institutions using this or equivalent equipment and discomfort levels. See appendix k for written instructions for subject's setting their own level of stimulation.

After application of the EEG cap and once midway between each condition participants will be administered (3) Visual Analog Scales, 1-indicating stress level, 2-indciating pain intensity and 3- indicating pain unpleasantness (see Appendices g).

Participants will be compensated $60 for participating in the full study and $10 for the first session only and will receive payment regardless early withdrawal from the study for any reason.

Additionally, participants will be offered to enter into a competition, based on accuracy and quickness during the working memory task. There will be 3 cash prizes: 1st prize-$150, 2nd prize-$100 and 3rd prize-$50.

Session 1- Screening; Subjects will complete five questionnaires (appendices b, c, d, e and f). Participants will then be asked to swirl 'Scope' mouthwash in their mouths for 30 seconds and then place the 'wash' in a small sterile tube for DNA analysis. Lastly, they will have two EEG electrodes attached to their ear lobes and two EEG scalp electrodes attached slightly above and back form their foreheads (frontal lobe). This will done as described above, except that only four electrodes will be attached and therefore the time to attach will be about 5 minutes and the time to record only 8 minutes, removal is less than two minutes.

Two to Three Weeks later- Session Two will take place

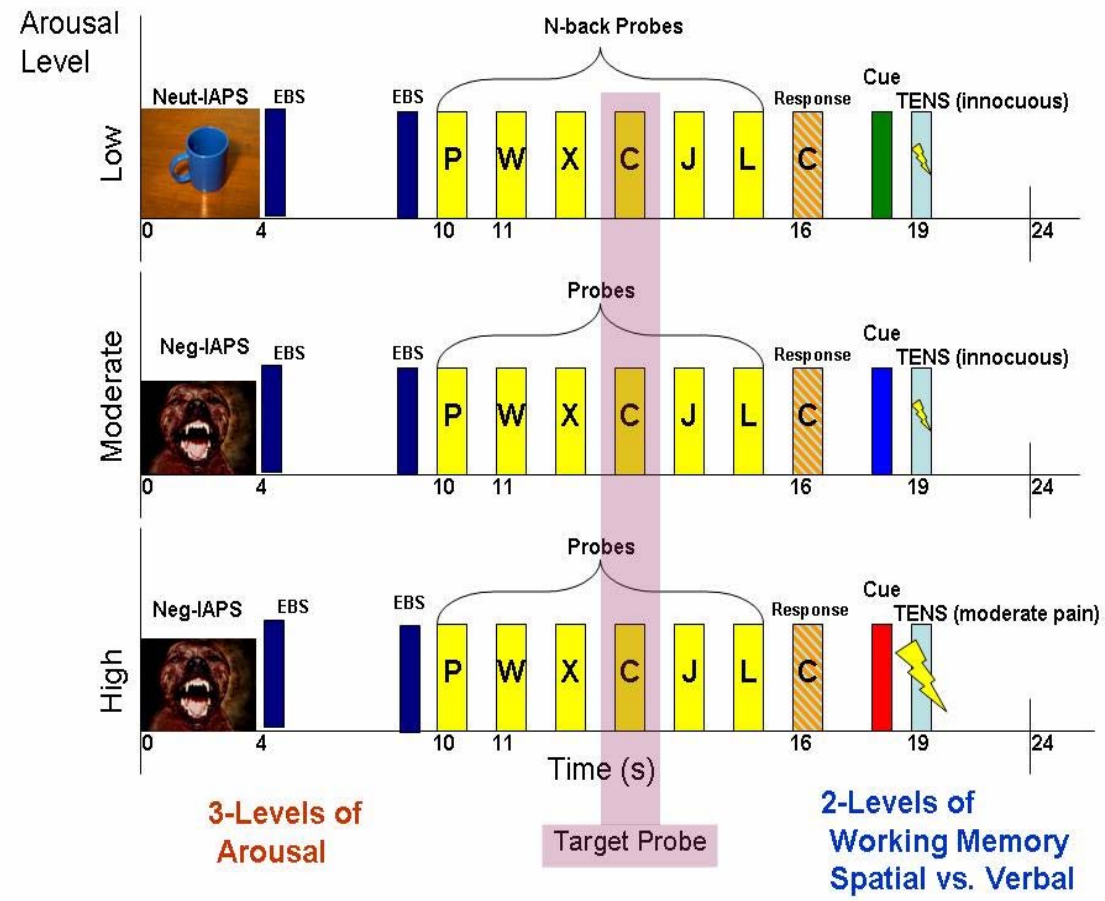

Figure 1 – Day Two Testing
1-Upper Row is the Low Arousal Condition
2-Middle Row is the Moderate Arousal Condition
3-Bottom Row is the High Arousal Condition
Note: a-EBS- is the acoustic startle probe
b- N-back probes- are the visual presentation of the letters that need to be remembered for the working memory task
c- the integers at the base of the each row represents time in seconds

d- Response- indicates the time of the response pad press by participant
e- Cue- is the visual presentation of a colored object-ex-circle that cues participants of the type of pending TENS stimulation
f- Photos at the start of every row are examples of actual images from the IAPS

Session 2, Phase 1 (Low & Moderate Arousal)- Inducement of emotional state, subjects will view pictures on projector screen at life-size scale selected from the international affective picture system (IAPS) that are designed to elicit emotional responses, picture contents for this study will range from neutral-picture of a telephone, to fearful-people pointing guns at others, snarling animals, or attackers holding knives to a victim's flesh with blood spilling. After the viewing of the picture participants will be shown a series of words or objects and then will be shown a single word or object and will be asked to hit a response button if that word or object was the same as the one viewed 2 pictures back in the series (called an N-back task).The three types of affect inducing stimuli (IAPS & TENS) will be classified for data processing as 1-low arousal (neutral), 2- moderate arousal (fearful) and 3-high arousal (fearful and nociceptive). Subjects will receive 80 trials of each stimuli type of approximate 20 second duration per trial, totaling about 55 minutes of task participation. Subjects will be given a 10-15 minute break between phase 1 & phase 2 while remaining in the EEG cap but they will be able to stand and stretch and get a small drink of water. Subjects will be asked to chew a small cotton plug at various times during session two to measure their cortisol levels.

Session 2, Phase 2 (High Arousal)- administration of moderate aversive electric stimulation, subjects will perform the same N-back task described above just prior to the administration of a moderate but aversive electric stimulation (when used properly, no tissue damage is typically reported in the literature and subjects will select their own level of stimulation to equal an uncomfortable-but bearable-moderately painful level only. Additionally, a reference list of other studies of this nature from major US research institutions will be available to subjects upon request. The electrode of the transcutaneous electric nerve stimulator (TENS) will be attached to the skin of the participant's non-dominant ankle in the same fashion described above for the heart rate monitoring electrodes. Subjects will receive <16- (2-5) second pulses of electric stimulation, which will be administered in a random order within an 80 trial block of stimuli-response. Subjects will perform an additional 20 working memory tasks without administration of any aversive stimuli. The total time of phase 2 will be approximately 30 minutes.

4. Risks and Benefits:

The current use of transcutaneous electric nerve stimulation (TENS) as a therapeutic agent in the repair of damaged nerves and/or tissue and as a post-surgical analgesic is widespread. It has been used therapeutically/clinically and researched for over 30 years. Because of its common therapeutic application across the US and its historically, no more than minimal risk profile, we ascertain that its use in this investigation is of no more than minimal risk to participants. It is used thousands of

times a day in clinical/physical therapy settings across the United States with no more than minimal risk and consequence.

The use of moderately painful stimuli in scientific investigation under the auspices of prudent IRBs' has at a minimum, a 10 year history of no more than minimal risk. The modalities used involve painful heat stimulation, moderate wrist or finger 'shock' (electric), CO_2 laser stimulation, cold pressor and TENS. All these modalities have been used responsibly and have demonstrated no more than minimal risk when used according to major research university protocol and IRB supervision. An abbreviated list of studies by major US research universities using various modalities from the above list, is enclosed as appendix j. Additionally enclosed as appendix i, are articles explaining specifically the use of TENS and the manufacturer's FDA approval letter.

Within the context of laboratory stressors: it is often cited in scientific review of relevant studies of stress induction, that the range of available laboratory stressors excluding the use of moderate nociception often fail to produce equivalent levels of 'real world stress' and therefore fall short of providing salient scientific information for use in future intervention. TENS is being used to successfully and safely induce arousal and stress in the subjects.

The administration of aversive electric stimulation (TENS) will cause discomfort and subject's may experience a temporary (a few hours) reddening of the skin around the area of the electrode placement.

Contraindications for TENS

1-TENS should not be used in patients with pacemakers or defibrillators as it could disrupt their function

2-TENS should not be used during pregnancy as it may induce premature labor—All female subjects who wish to participate must provide a negative pregnancy test-result-within one week of session two

3- TENS should not be applied over the carotid sinus (the neck) as it may cause acute lowering of blood pressure

4- TENS should not be applied anywhere over the neck as it may cause laryngospasm (contraction of the muscles of the voice box causing difficult breathing in but typically not effecting breathing out, it typically lasts 30-60 seconds.

5- TENS should not be placed in an area where one might have nerve or skin damage as burns could result

6- TENS should not be used on anyone with a history of Seizures / Epilepsy

Subjects will be given an instruction sheet to sign off on prior to administration of the TENS. The document explains how they may select their own level of discomfort via deciding the setting on the TENS unit.

There are minimal risks associated with the collection of EEG. As a result of wearing the electrode cap, the subject may experience a slight sensation or irritation of the skin as the scalp is lightly abraded. There is the possibility that the skin may be broken during abrading but this is rare. Our lab has been conducting research using EEG for over 30 years and has never reported an adverse incident. There are no known risks associated with the proper delivery of acoustic startle probes. There are

no known risks associated with the collection of the heart rate and skin conductance measures used in this study. There is also the possibility of fatigue as subjects will be tested for approximately two hours. There are no direct benefits conferred to participants, however, advances in psychological training may be generated by this study.

5. Confidentiality:

All information collected in this study will be kept confidential. Names will not be identified and only group-averaged results will be reported in publications and scientific presentations. Information will be kept in a locked cabinet in Room 2303A in the HLHP Building, UMCP, to which only research team members will have access. The list that links subject's names and ID numbers, Informed Consent forms and Sign-off documents will be kept in a locked box in Dr. Hatfield's office, to which only he and or his designee have access. Any information acquired during telephone screening on subjects that do not participate in either session one or two will be immediately destroyed. All data will be destroyed in 2017.

6. Information and Consent Form: See Appendix a

The following processes will be employed for obtaining informed consent:

a. Volunteers will read the Informed Consent Form (Appendix a) on day one and day two.
b. Volunteers will be asked if they fully understand the Informed Consent Form, and the risks and benefits of the study.
c. Volunteers will be asked if they have any conditions or reservations that would preclude their participation in the study. Those volunteers who have conditions or reservations about their ability to participate in the study will not participate in the study.
d. Volunteers will be asked if they have any questions about the Informed Consent Form, the research study, or their role in the research study.
e. Only after all questions have been answered will the research team member ask the volunteers to sign the Informed Consent Form.

7. Conflict of Interest: There are no known conflicts of interest in this research

8. Health Insurance Portability and Accountability Act (HIPAA) Compliance:
We are not using any protected or private health information in this study.

Appendix a

Informed Consent Form

INFORMED CONSENT FORM

Cognitive Motor Neuroscience Laboratory
Department of Kinesiology, University of Maryland College Park
May, 2007

Project Title: **Performance Under Pressure: Examination of Relevant Neurobiological and Genetic Influences**

Statement of Age of Participant: I hereby state that I am over 18 years of age, in good physical and emotional health, and would like to participate in a program of research being conducted by Dr. Bradley Hatfield and Ron Goodman of the Department of Kinesiology at the University of Maryland, College Park, Maryland 20742.

Purpose of the Research Project: The purpose of the current research is to study the relationship between brain activity and the quality of working memory under three levels of emotion/arousal.

Procedures Used: This study will involve two sessions, session two will be about 2-3 weeks after session one. The first session will be approximately 30 minutes. The second session will be approximately 2 hours and will be divided into two phases. You will be compensated $10 for participating in the first session (subjects that only participate in session one will receive a total of $10) and $50 for the second session and will receive payment regardless of early withdrawal from the study for any reason. ***Additionally, if you choose, you will be entered into a competition in which three participants will win cash prizes: 1st prize $150, 2nd prize $100 and 3rd prize of $50, for highest accuracy and quickness on the working memory task.*** In the first session you will sit in a comfortable chair, with your hands resting on a table. You will be asked to read and sign the consent form and you will be given a copy, additionally, you will be asked to fill out five

questionnaires: a health status questionnaire (HSQ), an inventory that assesses your handedness (EHI), an inventory that assesses your moods over the last few weeks (PANAS), a behavioral inventory (BIS/BAS) and an inventory that assesses your day-to-day level of anxiety (STAI). Examples of two items from one of the questionnaires are as follows-these questions refer to how you generally feel on a day to day basis: 1-I feel strained, 2-I feel self confident. When the forms have been completed you will be asked to swirl a small bottle of 'Scope' mouthwash in your mouth for 30 seconds and then place the 'wash' in a small sterile tube for DNA analysis. The DNA is analyzed for genotype on two specific genes known to be associated with emotion processing, so as to group participants for statistical analysis only. Note: we are not allowed to reveal your genotype. Additionally, you will be asked to chew a small cotton plug to measure your cortisol levels. Cortisol is a hormone that is associated with you current stress level. Lastly, on the first session you will be connected to two EEG (Electro-Encephalo-Gram-a test to measure brain waves) scalp electrodes and two ear-clip electrodes using the procedure outlined below for the second session, with the notable exception that only two electrodes will be attached and the process of attaching the electrodes will take approximately 10 minutes.

*Initials*_____*Date*_____

Procedures Used: During the second session you will be asked to sit in a comfortable chair, with your hands resting on a table. You will be asked to review and sign another copy of this consent form and fill out one questionnaire regarding exclusionary health conditions. During the entire session you will be asked to wear an EEG cap, similar to a swim cap. You will be asked to refrain from consuming any alcoholic beverages for 24 hours prior to your session. Additionally, you will be asked to refrain from eating, drinking large amounts of water (> 1 qt.) or consuming caffeinated beverages for at least one hour prior to the working memory task. You will be fitted for an EEG cap, similar to a swim cap that will be placed on your head. The purpose of the cap is to record

brain electrical activity. Electrodes will be placed on the skin above and below your left eye for the recording of eye blinks and clipped to your ear lobes to serve as a reference. These sensor sites will be lightly rubbed with a 3M plastic abrasive pad and then rubbed with alcohol and prepared with an FDA (Food and Drug Administration) approved non-toxic conducting gel that enables continuous connection between the skin of the scalp and the sensor or electrode surface. Your skin will be lightly rubbed at each electrode site with the blunt end of a wooden q-tip but the skin will not be broken. Using a blunt applicator and syringe, the previously described conducting gel will be applied to each electrode site. Again, the skin will not be broken. After the cap is prepared you will be asked a question and then requested to make a mark on a visual analog scale, which is nothing more than a line on the paper with each end representing the limits of a scale, for example: the question might be, How stressed do you feel, with one end of the scale saying, 'Not at all' and the other end saying 'completely,' you then place a mark on the line that approximates how stressed you are between the limits of the 'visual analog scale,' another question might be, How unpleasant was the sensation you just felt, and the ends of the scale might be 'neutral' and 'very unpleasant.' The questionnaire will take less than 5 minutes to complete. You will also be asked to chew the same type of small cotton plug as you did in session one at various times during the session. Additionally, 3 electrodes will be placed on your chest area near your heart in order to measure your heart rate and two small sensors will be placed on your non-dominant hand to record your skin electrical activity. You will be asked to wear headphones and at two different time intervals during each trial of the working memory task Electromyographic (EMG) measures of muscle tension will be collected from the EEG eyeblink electrodes after the delivery of a short burst of loud white noise (99 decibels, for $1/20^{th}$ of a second-an example of 99 decibel noise is a chain saw). This is known as an acoustic startle probe and is an index of emotion regulation that has been safely used in many studies by major research universities in the US. Lastly, two electrodes of a transcutaneous electric nerve stimulator(TENS) will be attached to the skin of your non-dominant foot/ankle as described for other

electrodes below. This form of stimulation is called transcutaneous electric nerve stimulation (TENS) and is used therapeutically for rehabilitation of damaged nerve tissue. During phase 1 of session two the stimulation delivered by the TENS unit will be completely painless and be equivalent to a blunt wooden object being lightly brushed across the skin. In phase one of session two you will view pictures on a projection screen selected

*Initials*_____*Date*_____

***Procedures Used*:** from the International Affective Picture System (IAPS) that are designed to elicit emotional responses, picture contents will range from neutral-picture of a telephone, to fearful-guns pointing at people, snarling animals and scenes depicting other fearful events such as an attacker holding a knife to a victim's flesh with blood spilling. After the viewing of the picture you will be shown a series of words or objects and then will be shown a single word or object and will be asked to hit a response button if that word or object was the same as the one viewed 2 pictures back in the series (called an N-back In phase two you will perform the same task just prior to the administration of a moderately painful electric stimulation. The TENS unit described above when turned up fully (we are not going to do this- as you will set your own level) causes uncomfortable-painful sensations but typically never reaches "unbearable" levels. The equipment is FDA approved. You will be asked to review and sign, an instruction sheet that asks you to select your own level of stimulation to equal a pain level equivalent to a 7 out of 11 on a scale with, 1 being no pain at all and 11 being unbearable, this is consistent with what has been done in previous studies at major U.S. research institutions The stimulation will last from two-five seconds and at any time, at your request, you may be immediately excused from any further stimulation. A reference list of other studies of this nature from major US research institutions will be available upon request. *We want to emphasize that the competition is completely optional and voluntary and that you may choose to withdraw from the competition at any time and that withdrawal from the competition*

will not affect your participation in the rest of the study and you will still receive your compensation. There is an approximate 1 in 10 to 1 in 12 chance of you winning money in this competition. If you win, you will be notified by both phone and email. Lastly, in the final condition in which the moderately painful TENS stimulation will be delivered there are 60-66 trials ***however****, you will receive the TENS simulation only between 8-18 times (how ever, this is random and you will not know on which trials the stimulation will be delivered). This does not differ either if you are in the competition, or you choose not to compete.*

Confidentiality: All information collected in the study is confidential; your name will not be identified at any time except for the Informed Consent and the form you sign to set the level of TENS stimulation. The data you provide will be grouped with the data of others for the purpose of reporting and presentation so that your individual data will not be identified. All data will be kept at the University of MD, in the HLHP Building Room 2303A in a locked cabinet to which only research team-members have access. The list that links your name to your ID number will be kept in a locked box in Dr. Hatfield's office, to which only he or his designee have access. All data will be destroyed 10 years after its analysis, in 2017.

Risks: You understand that the administration of moderately painful electric stimulation (TENS) will cause you discomfort to moderate pain and you may experience a temporary (a few hours) reddening of the skin around the area of the electrode placement. However, TENS is used safely and frequently in clinical and home settings across the USA.

Initials_____Date_____

Risks: **Situations and or Conditions when Subjects Should Not Participate:**

1-TENS should not be used in patients with pacemakers or defibrillators as it could disrupt their function

2-TENS should not be used during pregnancy as it may induce premature labor
3- TENS should not be applied over the carotid sinus (the neck/throat) as it may cause acute lowering of blood pressure
4- TENS should not be applied anywhere over the neck as it may cause laryngospasm (contraction of the muscles of the voice box causing difficult breathing in but typically not effecting breathing out, usually lasts 30-60 seconds.
5- TENS should not be used if one might have nerve or skin damage in the area of electrode placement as burns could result 6- TENS should not be used on anyone with a history of Seizure/Epilepsy
7-TENS should not be used on anyone with Asthma
8- TENS should not be used on anyone with Psychiatric illness
9-TENS electrodes should never be placed on the chest or head
You will select your own level of discomfort by you deciding the setting on the TENS unit but as mentioned before we ask that you approximate a 7 out of a 11on the scale that will be described to you on the instruction sheet you will be required to sign. Additionally, you understand that, as a result of wearing the EEG cap to measure brain electrical activity, you may experience slight sensations and irritation of the skin as the scalp is lightly rubbed at the electrode sites. There is a risk that your skin may be broken during EEG electrode preparation, however this is rare in our lab. Also note that a small number of people may be allergic to the conducting gel and or adhesive used on the throw away-single use electrodes but this is rare. Please let us know if you are experiencing irritation around electrode placement areas. There are no known risks associated with the measurement techniques used in this study to access Heart Rate, Skin Conductance, Muscle Tension (acoustic startle probe) or Cortisol levels. Even so, there are minimal risks to you if you participate in this study. There is a risk that some people may find the IAPS pictures disturbing. There is a possible risk that some people may find the white noise causes them discomfort. Lastly, there is a risk of fatigue since you will be wearing the EEG cap and performing the working memory task over a long period of time (1 1/2 - 2 hours). Again please note the 'Situations and

Conditions when Subjects Should Not Participate' above. If you are a female and wish to participate you must provide a negative pregnancy test-result within one week of session two.

Benefits: You understand that the experiment is not designed to help you personally but that the investigators hope to learn more about the mental processes involved in working memory performance in order to improve performance in others.

Initials_____Date_____

_

Freedom to Withdraw: You understand that you are free to ask questions about the study or to withdraw from the study at any time, without penalty. You understand that you will have a signed copy of this consent form given to you and that the investigators will provide you with the results of the study (however, genotypic information cannot be given out).

Where Medical Care is Available: You understand that the University of Maryland does not provide any medical care or hospitalization insurance coverage for participants in this research study, nor will the University of Maryland pay any medical expenses or provide any compensation for any injury sustained as a result of participation in this research study, except as required by law.

Informed Consent: *"I am voluntarily making a decision whether or not to participate in the research study described above. My signature indicates that I have decided to participate having read the information provided above and having had all of my questions answered. I will be given a copy of this consent form to keep.*

Printed Name of Participant_____

Signature of Participant_____

*Please check this space if you wish to be entered in the competition*_____

Signature of Witness_____

Date of Signatures_____

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If you have any questions about your rights as a research subject or to report a research-related injury you may contact:

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301-314-1475 (fax)
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Initials_____Date_____

Appendix b
Edinburgh Handedness Inventory

Subject ID_____ Date_____

EDINBURGH HANDEDNESS INVENTORY

Please indicate your preferences in the use of hands in the following activities *by putting + in the appropriate column.* Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, *put ++*. If in any case you are really indifferent *put + in both columns.* Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

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

		Left	Right
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking match (match)		
10	Opening box (lid)		
i.	Which foot do you prefer to kick with?		
ii.	Which eye do you use when using only one?		

Subject ID:_____
Date_____

Health Status Questionnaire

Date of birth _____ Age _____ Height _____ Weight _____

Hearing impairment Yes ____ No ____ If yes, describe
_____

Color blind Yes ____ No _____ Gender M _____ F _____

Years of education (high school = 12, + college = 16) _____

Current marital status: Married _____ Single _____ Widowed _____
Divorced_____

Are you, or is there any chance at all, you are pregnant_____

*If female and wish to participate you must provide proof of non-pregnant status, in the form of a negative pregnancy test-result within one week of Session Two*_____

*Are you presently experiencing, or have you ever experienced any nerve damage on your lower arms or legs*_____
*where*_____

*Are you presently experiencing, or have you ever experienced any abnormal skin or skin damage on either your lower arms or legs*_____
*where*_____

*Are you presently wearing and or using, or have you ever worn or used either a pacemaker or a defibrillator*_____

Do you currently or have you ever had any of the following medical disorders? Heart attack Yes ____ No ____Chest pain Yes ____ No __Hardening of the arteries Yes ____ No ____Irregular heart beat Yes ____ No ____Kidney disease Yes ____ No ____Diabetes Yes ____ No ____

Cancer Yes ____ No ____

Subject ID:_____

Blood clotting disorder Yes ____ No ____

Liver disease Yes ____ No ____

Asthma Yes ____ No ____

Lung disease Yes ____ No ____

Epilepsy or seizure disorder Yes ____ No ____

Psychiatric disorder Yes ____ No ____ if yes, what diagnosis _____

Migraine headaches Yes ____ No ____ if yes, frequency/intensity _____

Have you ever lost consciousness in the last 10 years?

Yes ____ No ____ if yes, when and why_____

Medications: Are you presently taking or have taken any of the following medications within the past two months?

Aspirin, Bufferin, Anacin Tranquilizers

Blood pressure pills Weight reducing pills

Cortisone Blood thinning pills

Cough medicine Dilantin

Digitalis Allergy shots

Hormones Water pills

Insulin or diabetic pills Antibiotics

Iron or blood medications Barbituates

Laxatives Phenobarbital

Sleeping pills Thyroid medicine

Subject ID:_____

Other medications not listed

_____

_____

__

Have you taken any non-prescription medications or drugs in the past two weeks?

Name what for? Dose/frequency last dose

1

2

3

List the name of any diseases, illnesses or accidents you have had which required hospitalization.

_____

_____

___

_____

___

Serious illnesses you have had not requiring hospitalization.

_____

_____

___

_____

___

Have you ever been told you have high blood pressure?

Yes ___ No ____ if yes, when _____

Do you have any other chronic illnesses or disabilities?

_____

__

Do you use tobacco products?

Yes ____ No ____ if yes, number of years
_____

Cigarettes ____ Pipe ____ Cigar ____ Chewing tobacco ____

Subject ID:_____

How many alcoholic drinks do you drink on any given day?
_____

(1 drink = 12 oz. Beer, 4 oz. Wine, or 1oz. Hard liquor)

How much caffeine do you drink on any given day?
_____

(number of cups of coffee, tea, cola; how many ounces)

Time since last intake of:

Caffeine _____

Tobacco _____

Alcohol _____

Appendix d
Spielberger Trait Anxiety Inventory

Self-Evaluation Questionnaire--Trait

Developed by Charles D. Spielberger
In collaboration with R. L. Gorsuch, R. Lushene, P. R. Vagg, and G. A. Jacobs

Subject ID#_____Date_____ .

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Not at all	Somewhat	Moderately so	Very Much so
1. I feel pleasant	1	2	3	4
2. I feel nervous and restless	1	2	3	4
3. I am satisfied with myself	1	2	3	4
4. I wish I could be as happy as others seem to be	1	2	3	4
5. I feel like a failure	1	2	3	4
6. I feel rested	1	2	3	4
7. I am "calm, cool, and collected"	1	2	3	4
8. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
9. I worry too much over something that really doesn't matter	1	2	3	4
10. I am happy	1	2	3	4
11. I have disturbing thoughts	1	2	3	4
12. I lack self-confidence	1	2	3	4
13. I feel secure	1	2	3	4
14. I make decisions easily	1	2	3	4
15. I feel inadequate	1	2	3	4
16. I am content	1	2	3	4
17. Some unimportant thought runs through my mind and bothers	1	2	3	4

me

18. I take disappointments so keenly that I can't put them out of my mind 1…..2…..3…...4
19. I am a steady person…… 1…..2…..3…...4

Appendix e
Positive and Negative Affect Schedule

a_PANAS form

Subject ID_____ Date_____

PANAS

Directions

This scale consists of a number of words that describe different feelings and emotions. Read each item and then circle the appropriate answer next to that word. Indicate to what extent you have felt this way during the past week/month.

Use the following scale to record your answers.

(1) = Very slightly or not at all (2) = A little (3) = Moderately (4) = Quite a bit (5) = Extremely

	Very slightly or not at all	**A little**	**Moderately**	**Quite a bit**	**Extremely**
1. Interested	1	2	3	4	5
2. Distressed	1	2	3	4	5
3. Excited	1	2	3	4	5
4. Upset	1	2	3	4	5
5. Strong	1	2	3	4	5
6. Guilty	1	2	3	4	5
7. Scared	1	2	3	4	5
8. Hostile	1	2	3	4	5
9. Enthusiastic	1	2	3	4	5
10. Proud	1	2	3	4	5
11. Irritable	1	2	3	4	5
12. Alert	1	2	3	4	5

13. Ashamed	1	2	3	4	5
14. Inspired	1	2	3	4	5
15. Nervous	1	2	3	4	5
16. Determined	1	2	3	4	5
17. Attentive	1	2	3	4	5
18. Jittery	1	2	3	4	5
19. Active	1	2	3	4	5

Appendix f
BIS/BAS Scales

a_BIS/BAS_form
b_BIS/BAS_General_Info

BIS/BAS scales

Several theorists have argued that two general motivational systems underlie behavior. A behavioral approach system (BAS) is believed to regulate appetitive motives, in which the goal is to move toward something desired. A behavioral avoidance (or inhibition) system (BIS) is said to regulate aversive motives, in which the goal is to move away from something unpleasant. We developed the BIS/BAS scales to assess individual differences in the sensitivity of these systems.

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology*, 67, 319-333. [abstract]

Here is how we administer the BIS/BAS scales here, followed by scoring instructions:

BIS/BAS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life._____

2. Even if something bad is about to happen to me, I rarely experience fear or nervousness._____

3. I go out of my way to get things I want._____

4. When I'm doing well at something I love to keep at it._____

5. I'm always willing to try something new if I think it will be fun._____

6. How I dress is important to me._____

7. When I get something I want, I feel excited and energized._____

8. Criticism or scolding hurts me quite a bit._____

9. When I want something I usually go all-out to get it._____

10. I will often do things for no other reason than that they might be fun._____

11. It's hard for me to find the time to do things such as get a haircut._____

12. If I see a chance to get something I want I move on it right away._____

13. I feel pretty worried or upset when I think or know somebody is angry at me._____

14. When I see an opportunity for something I like I get excited right away._____

15. I often act on the spur of the moment._____

16. If I think something unpleasant is going to happen I usually get pretty 'worked up.'_____

17. I often wonder why people act the way they do._____

18. When good things happen to me, it affects me strongly._____

19. I feel worried when I think I have done poorly at something important._____

20. I crave excitement and new sensations._____

21. When I go after something I use a "no holds barred" approach._____

22. I have very few fears compared to my friends._____

23. It would excite me to win a contest._____

24. I worry about making mistakes._____

Appendix g

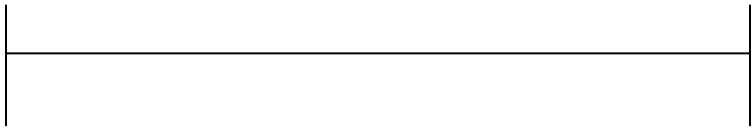
Visual Analog Scales

Subject # _____ Date_____ Trial # _____

Visual Analog Scale

Please put a vertical line through the rectangle at the point that best represents how you feel right now. The ends of each rectangle represent the opposite extremes of the **same** variable. Ex.

How ***Anxious*** do I feel?



Completely Anxious

Not anxious at all

Appendix h

Putnam et al, 1992

Appendix i
TENS INFORMATION

a_EMPI 'Select' User's Manual
b_FDA Approval Letter
c_TENS General Info Article
d_TENS Safety Guidelines Sign Off for Researchers
e_EMPI 'Select' Brochure

Transcutaneous Electrical Nerve Stimulation

Last Updated: January 26, 2007

Synonyms and related keywords: transcutaneous electrical nerve stimulation, TENS

AUTHOR INFORMATION Section 1 of 6 Next

Author Information Introduction Technical Considerations Applications Of Tens In Clinical Practice Comparison Between Tens And Other Electrical Modalities Bibliography

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and Rehabilitation, Loma Linda University School of Medicine

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Disclosure

Transcutaneous electrical nerve stimulation (TENS) currently is one of the most commonly used forms of electroanalgesia.

the use of TENS for various types of conditions such as low back pain (LBP), myofascial and arthritic pain, sympathetically mediated pain, bladder incontinence, neurogenic pain, visceral pain, and postsurgical pain. Because many of these studies were uncontrolled, there has been ongoing debate about the degree to which TENS is more effective than placebo in reducing pain.

The currently proposed mechanisms by which TENS produces neuromodulation include the following:

- Presynaptic inhibition in the dorsal horn of the spinal cord
- Endogenous pain control (via endorphins, enkephalins, and dynorphins)
- Direct inhibition of an abnormally excited nerve
- Restoration of afferent input

The results of laboratory studies suggest that electrical stimulation delivered by a TENS unit reduces pain through nociceptive inhibition at the presynaptic level in the dorsal horn, thus limiting its central transmission. The electrical stimuli on the skin preferentially activate low-threshold myelinated nerve fibers. The afferent input from these fibers inhibits propagation of nociception carried in the small unmyelinated C fibers by blocking transmission along these fibers to the target or T cells located in the substantia gelatinosa (laminae 2 and 3) of the dorsal horn.

The mechanism of the analgesia produced by TENS is explained by the gate control theory proposed by Melzack and Wall in 1965. The gate usually is closed, inhibiting constant nociceptive transmission via C fibers from the periphery to the T cell. When painful peripheral stimulation does occur, the information carried by C fibers reaches the T

cells and opens the gate, allowing pain transmission centrally to the thalamus and cortex, where it is interpreted as pain. The gate control theory postulated a mechanism by which the gate is closed again, preventing further central transmission of the nociceptive information to the cortex. The proposed mechanism for closing the gate is inhibition of the C-fiber nociception by impulses in activated myelinated fibers.

A TENS unit consists of one or more electric signal generators, a battery, and a set of electrodes. The units are small and programmable, and the generators can deliver trains of stimuli with variable current strengths, pulse rates, and pulse widths. The preferred waveform is biphasic, to avoid the electrolytic and iontophoretic effects of a unidirectional current. The usual settings for the stimulus parameters used clinically are the following:

- Amplitude - Current at low intensity, comfortable level, just above threshold
- Pulse width (duration) - 10-1000 microseconds
- Pulse rate (frequency) - 80-100 impulses per second (Hz); 0.5-10 Hz when stimulus intensity is set high

When TENS is used for pain control, patients are instructed to try different frequencies and intensities to find those that provide the best pain control for that individual. Optimal settings of stimulus parameters are subjective and are determined by trial and error. Electrode positioning is quite important. Usually, the electrodes are placed initially on

the skin over the painful area, but other locations (eg, over cutaneous nerves, trigger points, acupuncture sites) may give comparable or even better pain relief.

The 3 options for the standard settings used in different therapeutic methods of TENS application include the following:

- Conventional TENS has a high stimulation frequency (40-150 Hz) and low intensity, just above threshold, with the current set between 10-30 mA. The pulse duration is short (up to 50 microseconds). The onset of analgesia with this setup is virtually immediate. Pain relief lasts while the stimulus is turned on, but it usually abates when the stimulation stops. Patients customarily apply the electrodes and leave them in place all day, turning the stimulus on for approximately 30-minute intervals throughout the day. In individuals who respond well, analgesia persists for a variable time after the stimulation stops.
- In acupuncturelike settings, the TENS unit delivers low frequency stimulus trains at 1-10 Hz, at a high stimulus intensity, close to the tolerance limit of the patient. Although this method sometimes may be more effective than conventional TENS, it is uncomfortable, and not many patients can tolerate it. This method often is considered for patients who do not respond to conventional TENS.
- Pulsed (burst) TENS uses low-intensity stimuli firing in high frequency bursts. The recurrent bursts discharge at 1-2 Hz, and the frequency of impulses within each burst is at 100 Hz. No particular advantage has been established for the pulsed method over the conventional TENS method.

Patient comfort is a very important determinant of compliance and, consequently, the overall success of treatment. The intensity of the impulse is a function of both pulse duration and amplitude. Greater pulse widths tend to be more painful. The acupuncturelike method is less tolerable because the impulse intensity is higher.

The amount of output current depends on the combined impedance of the electrodes, skin, and tissues. With repetitive electrical stimuli applied to the same location on the skin, the skin impedance is reduced, which could result in greater current flow as stimulation continues. A constant current stimulator, therefore, is preferred to minimize sudden uncontrolled fluctuations of current intensity related to changes in impedance. An electroconductive gel applied between the electrode and skin serves to minimize the skin impedance. Skin irritation can occur in as many as 33% of patients, at least in part, due to drying out of the electrode gel. Patients need to be instructed in the use and care of TENS equipment, with particular attention to the electrodes.

Medical complications arising from use of TENS are rare; however, skin irritation is a frequent problem and often is due partly to the drying out of the electrodes. Sometimes individuals react to the tape used to secure the electrodes. Skin irritation is minimized by using self-adhesive disposable electrodes and repositioning them slightly for repeated applications. The use of TENS is contraindicated in patients with demand-type pacemakers because their stimulus outputs may drive or inhibit the pacemaker.

A variety of newer transcutaneous or percutaneous electrical stimulation modalities recently has emerged.

- Interferential current therapy (IFC) is

based on summation of 2 alternating current signals of slightly different frequency. The resultant current consists of cyclical modulation of amplitude, based on the difference in frequency between the 2 signals. When the signals are in phase, they summate to an amplitude sufficient to stimulate, but no stimulation occurs when they are out of phase. The beat frequency of IFC is equal to the difference in the frequencies of the 2 signals. For example, the beat frequency and, hence, the stimulation rate of a dual channel IFC unit with signals set at 4200 and 4100 Hz is 100 Hz.

- IFC therapy can deliver higher currents than TENS. IFC can use 2, 4, or 6 applicators, arranged in either the same plane for use on regions such as the back or in different planes in complex regions (eg, the shoulder).
- Percutaneous electrical nerve stimulation (PENS) combines advantages of both electroacupuncture and TENS. Rather than using surface electrodes, PENS uses acupuncturelike needle probes as electrodes, placed at dermatomal levels corresponding to local pathology. The main advantage of PENS over TENS is that it bypasses the local skin resistance and delivers electrical stimuli at the precisely desired level in close proximity to the nerve endings located in soft tissue, muscle, or periosteum.

Literature on the use of TENS in a variety of medical conditions reports a wide range of outcomes, from very positive to negative effectiveness. Currently, there is an overall consensus favoring the use of TENS, with authorities differing on its value in different clinical situations. Generally, TENS provides initial relief of pain in 70-80% of patients, but the success rate decreases after a few months or longer to around 20-30%. To exclude a false-negative response, a trial of TENS for at least 1 hour should be given to confirm potential benefit from subsequent continuous use.

According to Johnson, the time from the start of stimulation to the onset of analgesia varies from almost immediate to hours (on average 20-30 minutes in over 75% of patients and 1 hour in 95% of patients). The duration of analgesia also varies considerably, continuing only for the duration of stimulation in some patients and providing considerable prolonged poststimulation relief in others. The same TENS protocol may have different degrees of antinociception in acute experimental pain compared with chronic clinical pain in patients with chronic LBP.

Patients differ in their stimulus preferences and in their rates of compliance. In Johnson's study of compliance in patients who benefited from TENS, 75% used the device on a daily basis. Patients showed individual preferences for particular pulse frequencies and patterns and consistently adjusted their stimulators to these settings on subsequent treatment sessions.

Indications for the use of TENS

- Neurogenic pain (eg, deafferentation pain, phantom pain), sympathetically mediated pain, postherpetic neuralgia, trigeminal neuralgia, atypical facial

pain, brachial plexus avulsion, pain after spinal cord injury (SCI)

- Musculoskeletal pain: Examples of specific diagnoses include joint pain from rheumatoid arthritis and osteoarthritis, acute postoperative pain (eg, postthoracotomy), and acute posttraumatic pain. After surgery, TENS is most effective for mild-to-moderate levels of pain, and it is ineffective for severe pain. The use of TENS in chronic LBP and myofascial pain is controversial, as placebo-controlled studies fail to show statistically significant beneficial results. Uncertainty also exists about the value of TENS in tension headache.
- Visceral pain and dysmenorrhea are other conditions in which TENS has been applied successfully.
- Other disorders: TENS has been used successfully in patients with angina pectoris and urge incontinence, as well as in patients requiring dental anesthesia. Reports discuss use of TENS to assist patients in regaining motor function following stroke, to control nausea in patients on chemotherapy, as an opioid-sparing modality in postoperative recovery, and in postfracture pain.

Contraindications for the use of TENS

- TENS should not be used in patients with a pacemaker (especially of the demand type).
- TENS should not be used during pregnancy because it may induce premature labor.
- TENS should not be applied over the carotid sinuses due to the risk of acute hypotension through a vasovagal reflex.
- TENS should not be placed over the

anterior neck because of possible laryngospasm due to laryngeal muscle contraction.
- The electrodes should not be placed in an area of sensory impairment (eg, in cases of nerve lesions, neuropathies), where the possibility of burns exists.
- A TENS unit should be used cautiously in patients with a spinal cord stimulator or intrathecal pump.

COMPARISON BETWEEN TENS AND OTHER ELECTRICAL MODALITIES

A number of studies have compared TENS to other similar therapeutic modalities, including PENS, IFC, and acupuncture.

- In one study of elderly patients with chronic LBP, both acupuncture and TENS had demonstrable benefits, with the acupuncture group demonstrating improvement in spinal flexion.
- In patients with chronic LBP and sciatica, PENS was more effective than TENS in providing short-term pain relief and improved function, including an improved quality of sleep and sense of well-being.
- Overall, 91% and 73% of patients, respectively, chose PENS as the preferred modality for pain relief in LBP and sciatica.
- PENS has been used successfully for pain relief in patients with acute herpes zoster and cancer with bony metastases.
- Both IFC and TENS had a statistically significant effect on median nerve excitation threshold in young women.

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Appendix j
List of References of Major Research Institutions using Aversive/Nociceptive Stimuli in Recent Studies

List of Major US Research Institutions using Pain Induction in IRB Approved Research

1-Shackman, A. J., Sarinopoulos, I, Maxwell, J. S., Pizzagalli, D. A., Lavric, A., & m Davidson, R. J. (2006), Anxiety selectively disrupts visuospatial working memory, *Emotion*, 6, 40-61.

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4-Vogt BA, (2005), Pain and Emotion Interactions in Subregions of the Cingulate Gyrus, *Nature Reviews Neuroscience*, Vol. 6, 533-544.

5-Wager TD, et al, (2004), Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain, *Science*, Vol. 303, 1162-1167

6-Phelps EA, Delgado MR, Nearing KL, LeDoux JE, (2004), Extinction Learning in Humans: Role of the Amygdala and vmPFC, *Neuron,* Vol. 43897-905.

7-Seminowicz DA, Mikulis DJ & Davis KD, (2004), Cognitive Modulation of pain related brain responses depends on behavioral strategy, *Pain*, 112, 48-58

8-Price DD, Barrelo JJ & Rainville P, (2002), Integrating experiential-phenomenological methods and neuroscience to study neural mechanisms of pain and consciousness, *Consciousness and Cognition* 11, 593-608

9-Tracey I, et al, (2002), Imaging Attentional Modulation of Pain in the Periaqueductal Gray in Humans, *The Journal of Neuroscience*, 22(7), 2748-2752

10-Petrovic P, Ingvar M, (2002), Imaging cognitive modulation of pain processing, *Pain*, 95, 1-5

11-Lorenz J, Minoshima S, Casey KL, (2003), Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation, *Brain*, 126, 1079-1091

12-Giordano J, (2005), The Neurobiology of Nociceptive and Anti-Nociceptive Systems, *Pain Physician*; 8:277-290

13-Voegelin MR, Zoppi M, Meucci R, Jafranesco D, & Bartoli A, (2003), Factors Influencing pricking pain threshold using a CO_2 laser, *Physiologic Measurement*, 24, 57-73

14-Plaghki L, Mouraux A, (2006), EEG and laser stimulation as tools for pain research, *Current Opinion in Investigational* Drugs 6(1),: 58-64

15-Christopher deCharms R, et al, (2005), Control over brain activation and pain learned by using real-time fMRI, *Proceedings of the National Academy of Science*, vol. 102, no. 51, 18626-18631

16-Borsook D & Becerra LR, (2006), Breaking down barriers: fMRI applications in pain, analgesia and analgesics, *Molecular Pain*, 2:30, 2-40

17-Bantick SJ, et al, (2002), Imaging how attention modulates pain in humans using functional MRI, *Brain*, 125, 310-319

18-Babiloni C, et al, (2004), Cortical Sensorimotor Interactions During the Expectancy of a Go/No-Go Task: Effects of Painful Stimuli, *Behavioral Neuroscience*, vol. 118, no. 5, 925-935

19-Mouraux A & Plaghki L, (2006), Are the processes reflected by the late and ultra-late laser evoked potentials specific to nociception, Supplement to- *Clinical Neurophysiology,* vol. 59, Chapter 27, 197-204

20-Moulton EA, Keaser ML, Gullapalli RP & Greenspan JD, (2005), Regional Intensive and temporal patterns of fMRI activation distinguishing noxious and innocuous contact heat, *Journal of Neurophysiology*, Apr;93(4): 2183-93 From: Program of Neuroscience, University of Maryland, Baltimore, MD 21201

There are of course hundreds of studies by major US research institutions involving the use of painful stimuli, more resources may be listed upon request.

Appendix k
Instructions for Participants to set level of Discomfort for TENS

Instructions for Participants to set level of Discomfort for TENS

The piece of equipment that you are about to be connected to, is called a transcutaneous electric nerve stimulator (TENS). This unit is typically used for therapeutic intervention in clinical settings to help induce nerve repair and alleviate pain in people that have suffered tissue damage. The stimulation itself when used properly has been administered safely by both clinicians and patients, as already mentioned it is used for remedial reasons many times daily in clinical and home settings in the USA. However, it should be noted that if the intensity setting is turned up it may cause discomfort or moderate pain, you may experience a temporary (few hours) reddening of the skin around the electrode placement. Additionally, we ask that you have carefully read the 'Risks section' of the Consent Form and the 'Day Two Exclusionary Review' questionnaire in regards to the Situations and Conditions when TENS should not be used.

For the purposes of this scientific investigation, we will ask you to set your own level of stimulation. Additionally, we want you to use the following guidelines to accomplish this.

1-Use a scale of 1 through 11, with 1 -being no pain at all, and 11 -being the worst pain you can imagine:
2-Please set your level to be equivalent to what you believe to be a 7 on the scale described above, 7 should be barely tolerable; it should be likened to extreme discomfort and a feeling you want to avoid and or 'turn off'—but should not be unbearable-intense pain
3-Remember you may ask to withdraw from this protocol at anytime and we ask you to please let us know if you are feeling any stress that you feel may be out of your control and we will cease the protocol immediately
4- A visual cue of a red circle will appear on the screen before the trials in which you will receive the stimulation, however you may not receive stimulation on every-single trial preceded by a red circle. In other words, after you see a red circle you may or may not receive stimulation but there is no way of you knowing if the stimulation will be delivered as it will be done randomly.
5-Information regarding 1-the electrical specifications, 2-FDA approval of the equipment and 3-an abbreviated list of major research universities that have induced pain under supervision of Institutional Review Boards during scientific investigation, is available upon request and has been submitted to the Institutional Review Board that approved this scientific investigation.

6- Please if you have any questions or do not fully understand, speak up now.

Thank You.

Date_____

Signature of Participant, indicates that you have read and understand these instructions.

Appendix m
a_Recruitment Flier
b_Telephone Script for Screening Recruits

Participants Needed for Fall Study
$60 for full study or
$10 for initial screening only
ONE-30 Minute Visit ONE-2-Hour Visit
Optional Competition 3 Prizes, $150, $100 & $50

This Study Involves Electroencephalography (EEG) and Heart Rate Monitoring, Genotyping and Electric Nerve Stimulation. We take physiologic measures of one's ability to perform a working memory task under stress. *Challenging and Engaging*

If you are pregnant, have a pacemaker, have a defibrillator, have any heart disease, have a history of seizures/epilepsy, have skin or nerve damage on your lower legs, have asthma, have any major organ illness or any history of psychiatric illness (ex-panic attacks) you will be not be allowed to participate in this study. Additionally, you must be between the ages of 18-35 and be right-handed in order to participate.

1st Visit—25-35 minutes –Review & Sign Consent, Fill out Questionnaires, & One Mouthwash Rinse for genotyping, & 15-20 minutes-Attach Two EEG electrodes and Record 8 minutes of brain wave activity

---

2-3 Weeks Later
2nd Visit---2 Hours—Full EEG recording, Working

Memory Task and Electric Nerve Stimulation

Contact:
Ron Goodman
rongo324@aol.com
301-405-6872

Reference---Performance Under Pressure Study

Telephone Script for Screening of Participants

"Performance Under Pressure" Date_____ Interviewer Initials_____

1- Hello, are you interested in the "Performance Under Pressure Study"_____

2- I need to tell you a few things about the study—

1- First there are two sessions and the Second session is 2-3 weeks after the first One_____

2- There are exclusionary criteria and not everyone will take part in the second session of the study, the reasons for this have to do with the data analysis and you will be informed of this about two weeks after the first session_____

3- Additionally there are health status exclusionary criteria, these include—

a- If you are pregnant you may not take part in the study and all females that wish to participate will be required to provide a negative pregnancy test-result within one week of day two testing_____

b- If you have any history of heart problems of any kind and have ever or are now using a pacemaker or defibrillator_____

c- Have any history of seizures/epilepsy_____

d- Have any abnormal skin, skin damage or nerve damage to your lower legs_____

e- Have any major organ illness_____

f- Have Asthma_____

g- Have any history of psychiatric illness_____

h- Are you right-handed

4- You will receive $10 for the first session and $50 for the second session if you are asked to return and agree_____

a-Additionally, there is an optional competition, the details of which will be given at the time of acceptance into the study._____

5-Prior to each testing session we ask that you refrain from consuming any alcohol on the day of testing. Additionally, we ask that you refrain from eating, brushing your teeth, or drinking caffeinated beverages or large amounts (>1 Qt.) of water/liquid for at least one hour prior to testing in order to enable valid salivary cortisol (i.e., stress hormone) samples.

6- Do you wish to participate_____?

7- Could you please give me your name, phone number and email address, thank you_____

Name:

_____

Phone Number:

_____

Email Address:

_____

Appendix n

a_Acoustic Startle Probe Equipment Information & Safety Specifications
b_Committee Report: Guidelines for human startle eyeblink electromyographic studies

Committee report: Guidelines for human startle eyeblink electromyographic studies

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Abstract
The human startle response is a sensitive, noninvasive measure of central nervous system activity that is currently used in a wide variety of research and clinical settings. In this article, we raise methodological issues and present recommendations for optimal methods of startle blink electromyographic (EMG) response elicitation, recording, quantification, and reporting. It is hoped that this report will fostermore methodological validity and reliability in research using the startle response, as well as increase the detail with which relevant methodology is reported in publications using this measure.

Descriptors: Startle, Blink, Electromyographic (EMG), Human

Due to the dramatic increase in the use of the startle blink response in research and clinical settings, Gregory Miller, then Editor of Psychophysiology (2001), appointed a committee to consider guidelines for startle blink research in humans. The result is this article, the aim of which is to propose a series of suggestions that might guide researchers in the collection and reporting of data based on the blink component of the startle response. Due to space limitations, this article will not deal with several areas of interest to startle researchers, such as affect, attention, psychopathology, and prepulse inhibition, but will instead focus on the fundamental methodology applied when startle blink electromyographic (EMG) data are used to investigate any research question. One goal of this article is to bring a higher degree of both reliability and validity to this research area by summarizing recent research in which alternative methods have been compared and by providing criteria for choosing among them. Another goal is to encourage the reporting of relevant

methodological details in publications in this area of research. We hope that this article will serve as a guide for researchers new to the area of startle, showing them the potential ramifications of deciding to do things one way rather than another. Moreover, experienced researchers may benefit from a review of the methodological advances that have been made in this area over the past few years, and may even reconsider some of their current practices.

Blink as a Measure of Startle

The startle response consists of several components, including the eyeblink reflex, one of the first measures developed in experimental psychology (Exner, 1874; see Dawson, Schell, & Bo¨hmelt, 1999, for a brief historical background). Whereas most of the measurement methods used in the early studies, such as the high speed camera images employed by Landis and Hunt (1939) or Dodge's pendulum-photochronograph method (Gormezano, 1966), have been resigned to the museum of psychological methodologies, several different approaches to the measurement of blink responses are still in use. Some of these are used to measure eyelid movement, including potentiometric, photoelectric, vertical electrooculographic (vEOG), and magnetic search coil methods. Others are used to measure action potentials generated within the orbicularis oculi muscle (the muscle that closes the eye during a blink), with surface or needle electromyographic (EMG) recording electrodes. Currently, surface EMG is the most frequently used measure in human startle blink research. It has been shown, however, that alternative methods provide very similar results in most cases (see Clarkson & Berg, 1984, comparing vEOG and potentiometric [mechanical] recordings; Flaten, 1993, comparing EMG and photoelectric measures; and Gehricke, Ornitz, & Siddarth, 2002, comparing EMG and vEOG measures).

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1 For precise measurement of lid movement, there is general agreement among oculomotor physiologists thatmagnetic search coils constitute the best available technology (e.g., Evinger & Manning, 1993). However, most psychophysiologists record blinks not to understand their kinematics and underlying motor physiology, but to investigate reflex elicitation and modification by psychologically interesting factors and manipulations. For this purpose, EMG has become the generally preferred method. EMG offers several experimental advantages over the magnetic search coil method, such as requiring less expensive equipment and less obtrusive sensors. Further, EMG is more sensitive to blink activity than are measures of actual lid movement (Flaten, 1993), because EMG recordings can detect weak contractions of orbicularis oculi that are not sufficient to overcome the inertia of the eyelid. In addition, EMG is capable of portraying distinct subcomponents of muscle activation (e.g., the R1, R2, and R3 components of the trigeminally elicited blink; Kimura et al., 1994; Penders & Delwaide, 1973) as well as the silent period that follows intense orbicularis

oculi activation.

Participant Preparation

Blink responses are measured by placing two electrodes on the skin surface overlaying the orbicularis oculi muscle, with the EMG signal then conducted to the recording equipment. It is crucial that this EMG signal be measured with as much sensitivity and fidelity as possible, a process that begins at the surface of the skin (Fridlund & Cacioppo, 1986).

Skin Preparation

Because startle blink EMG is a rather small biosignal (amplitude is rarely more than a few hundred microvolts), recording conditions shouldmaximize the flow of current fromthe skin surface to the conductive surface of the electrodes. The goal of skin preparation is to reduce the impedance between skin surface and electrode gel, by removing makeup, skin oil, and dead skin cells without causing undue discomfort and potential risk to the participant or experimenter. Although there aremany techniques for preparing the blink EMG recording site, the most common methods involve rubbing the skin briskly with a gauze pad and cleansing the site with either soap and water or alcohol (with the participant's eyes closed to minimize eye irritation caused by evaporating fumes). Some researchers then massage a thin layer of nonabrasive electrode gel into the recording site. Excess gel that remains on the skin surface should be wiped off, because residual gel may create a conductive bridge between the two electrodes, creating an electrical shunt that would weaken or eliminate the recorded EMG signal. Use of abrasive gels or pads is not recommended, because they may be too harsh for the sensitive skin around the eyes, and because the startle response is sensitive to negative affect. Any abrasive preparation that poses the risk of skin penetration should be conducted following the Society's Guidelines for Reducing the Risk of Disease Transmission in the Psychophysiological Laboratory (Putnam, Johnson, & Roth, 1992).

Electrode Preparation, Location, and Attachment

Orbicularis oculi is a striated sphincter muscle encircling the orbital fissure, with distinct fast- and slow-twitch portions (Gordon, 1951). Although smallEMGelectrodes placed at the base of the upper eyelid are optimal for isolating reflexive muscle contractions from other activity, practical difficulties such as intrusive skin preparation, electrode weight, and motion artifacts during lid movement render upper lid EMG measurement impractical. In most settings, recording electrodes are placed below the lower lid, overlaying the orbital slow-twitch portion of the orbicularis oculi.

Figure 1 shows the electrode placement employed in the majority of studies that record blinkEMGfromthe orbicularis oculi muscle. A typical configuration consists of one electrode placed below the lower eyelid in line with the pupil in forward gaze, a second electrode placed approximately 1–2 cm lateral to the first (center-to-center), and a signal ground electrode (also referred to as an isolated ground, not to be confused with an earth ground) attached at an electrically inactive site such as the forehead, mastoid, or temple. It should be noted, however, that facial anatomy varies widely across individuals and that optimal placement of the electrodes relative to the muscle may require individual adjustments of electrode placement. Most published reports state that electrodes are attached under the left eye (probably because the majority of researchers are right-handed, and the left side of the participant's face is more accessible for electrode placement). With binaural stimulation, laterality effects are not significant (Bradley, Cuthbert, & Lang, 1996; but see

Hawk & Cook, 1997).
The preferred electrodes are Ag/AgCl miniature electrodes, in which the contact surface (diameter of less than 5mm) is recessed within a plastic casing having an external diameter of less than 15mm.Electrodes should be filled with a high-conductivity electrode gel and attached with double-sided adhesive collars. These collars can be trimmed with scissors so that the electrodes can be placed very close to the lower eyelid without interfering with

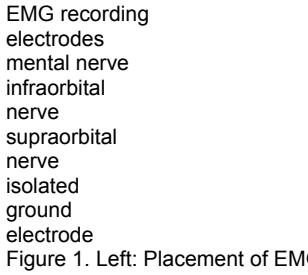

Figure 1. Left: Placement of EMG recording electrodes over the lower orbital portion of the orbicularis oculi muscle. The isolated ground electrode is placed on the forehead. Right: Electrodes for electrical stimulation of the three chief cutaneous branches of the trigeminal nerve. Solid black circles indicate cathodes placed over the nerve branches at the site of their emergence through the supraorbital, infraorbital, and mental foramina. Gray circles indicate anodes.
natural eyelid movement and without touching the lower lid or eyelashes. Trimming of the collars also allows the electrodes to be placed closer together, although collars should not overlap, because thismay allow mechanical artifacts due to skinmovement.
If disposable electrodes that are prepackaged with recording gel are used, caution must be taken because these electrodes can dry out, a problemthat can be solved by adding a little conductive gel to the electrode. Reusable electrodes should be cleaned thoroughly and disinfected before they are used with a different participant (see Putnam et al., 1992), avoiding removal of any portion of the AgCl layer.
Electrode impedance should be checked with each recording electrode in a circuit with the signal ground electrode, to confirm good and equal contact across the measurement electrodes. High impedance (above 5000 O; Cacioppo, Tassinary, & Fridlund, 1990), and unequal electrode impedances are to be avoided as they attenuate the recorded signal and limit its quality by permitting intrusion of electromagnetic interference. If electrode impedances are not satisfactory, then electrodesmay be removed and skin preparation and electrode attachment repeated.
After checking electrode impedances, the EMG signal should be checked for noise artifacts that would obscure the blink reflex. These noise sources include intrusions fromphysical sources such as interference from power lines (50 or 60 Hz interference), from the startle eliciting stimulus itself, or from other biosignals such as ECG or EMG from other facial muscles. An ideal recording should have a minimal amount of tonic noise and show patterns of orbicularis oculi activation during spontaneous and voluntary blinks that are clearly distinguishable from ongoing tonic activity. High noise levels or a failure to detect spontaneous blinks may require a change of electrode placement (although the possibility of a defective electrode should also be considered). A complete absence of adequate recording of spontaneous or voluntary blinks suggests a problem with the recording equipment.
In any case, the participant in such a situation should not be labeled a nonresponder, a classification that should be reserved for participants from whom spontaneous and voluntary blinks are clearly apparent, but who fail to exhibit a startle response

on a predetermined number of presentations of the startle stimulus (see the section ‘‘Rejection of Trials and Participants’’ below).

EMG is differentially amplified (see the section ‘‘Amplification’’ below), which means that the amplifier outputs the difference between the signals that reach the two active electrodes and rejects signals that are common to the two electrodes (common mode rejection). Although modern amplifiers are very good at removing noise, other precautions, such as recording in an electrically shielded environment (Faraday cage), use of equipment that emits low levels of electromagnetic noise, or use of notch filters to reduce power line interference (50 or 60 Hz), can enhance the quality of the EMG recording. However, notch filters have the disadvantage of suppressing both the EMG signal and noise in the 50 or 60 Hz range. Thus, it is preferable to record under conditions that minimize 50/60 Hz noise intrusions so that a notch filter is not required. If this is not possible, a filter can be used, but it is likely to result in an underestimation of EMG activity to the extent that there is signal in the frequency range of the notch filter. Noise intrusions can also be reduced by the use of shielded electrode wires or by loosely braiding the electrode wires together, which makes it more likely that both electrodes pick up noise equally (which would be eliminated during differential amplification).

The Data Acquisition Session

Participants are usually asked to sit quietly and to refrain from moving. To minimize movement artifact, participants are typically asked to look toward some object or general area in front of them. The choice of object or area (fixation point, picture, silent movie, a wall or door) depends on the nature of the experiment, because attentional manipulation may affect startle or its modification (Filion, Dawson, & Schell, 1998). A second approach is to ask participants to close their eyes during the recording session (Hawk, Stevenson, & Cook, 1992; Sanes, 1984), although this may lead to drowsiness and falling asleep. A third approach is to record eye movements explicitly with vEOG and hEOG (horizontal EOG), and to exclude contaminated trials. Finally, the experimenter may wish to observe the participant on a closedcircuit video monitor, noting overt movement and state changes during the testing session.

Startle Elicitation

Acoustic Stimulation

Stimulus properties. The blink reflex can be influenced by several parameters of a single eliciting stimulus, including bandwidth, intensity, rise time, and duration (see Berg & Balaban, 1999). Whenmultiple eliciting stimuli are presented, the response can also be influenced by stimulus number and interstimulus interval. The method by which the stimulus is generated and presented to the subject can also influence the startle responses that are recorded. Therefore, it is recommended that researchers report relevant aspects of stimulus composition, generation, and presentation in appropriate detail.

With regard to stimulus bandwidth, the most commonly used acoustic startle stimulus is broadband (white) noise, which is generated to contain frequencies in the 20 Hz to 20 kHz range (although a narrower range of frequencies may actually be presented, due to limitations in frequency responsiveness of the sound production equipment). When other parameters are equal, noise is a more effective startle stimulus than is pure tone (Blumenthal & Berg, 1986a; Blumenthal & Goode, 1991), with responses following noise stimuli resulting in higher response magnitude, probability, and amplitude, and shorter onset latency

(see the section ‘‘ResponseQuantification’’ below for a definition of these response measures).

In general, increasing the intensity of acoustic startle stimuli has the effect of increasing response magnitude, probability, and amplitude and decreasing response onset latency. This effect has been found in studies focusing on parametric variations in simple presentations of startle stimuli (e.g., Blumenthal, 1988, 1996; Blumenthal & Berg, 1986a), as well as startle stimuli presented in the context of a foreground task (Cuthbert, Bradley, & Lang, 1996). Berg (1973), using a psychophysical threshold determination procedure andmeasuring lidmovement with amechanical recording device (lid potentiometer), reported that the 50% probability threshold for a blink response was 85 dB(A) SPL. In part due to this result, a preponderance of acoustic startle studies have employed intensities in the range of 100 dB(A) SPL or more. However, Blumenthal and Goode (1991) demonstrated that startle responses could be obtained with broadband stimuli in the range of 50 to 70 dB(A) SPL. This implies that prepulses and other lead stimuli in this intensity range may elicit startle blink responses on some trials (Dahmen & Corr, 2004). This also implies that very high stimulus intensities may not be necessary

for the reliable elicitation of the blink response. A moderately intense stimulus would be expected to produce a response that is intermediate between the floor and ceiling of the dynamic range of the startle response, allowing for maximal sensitivity of the response to a variety of experimental factors.

An advantage of using less intense eliciting stimuli is the minimization of risk to participants fromunnecessarily high acoustic stimulus intensities. The United States Occupational Safety and Health Act standards (OSHA standard number 1910.95) state that, at a stimulus intensity of 105 dB(A) SPL, hearing protection is not required unless the sound is continuous for 1 h. However, this refers to continuous stimulation, not to impulse stimuli, such as those used to elicit startle. Although a 50-ms-duration stimulus at 105 dB SPL would still be well below the level that OSHA regards as unsafe, less intense stimuli are likely to be less aversive for most subject groups. The comfort of the participant is certainly a relevant concern, given the sensitivity of the startle response to negative affect (Bradley, Cuthbert, & Lang, 1999).

Startle responses are also influenced by stimulus rise time, a measure of how quickly the stimulus reaches its full, steady-state amplitude. Startle stimuli with shorter rise times elicit responses with higher probability, larger magnitude and amplitude, and shorter onset latency (Blumenthal, 1988), presumably because startle is specialized for the detection of sudden change in the environment (Blumenthal & Berg, 1986a; Graham, 1992). In principle, even the fastest rise time must have some finite value, although many researchers report the rise time as ‘‘instantaneous’’ when the output of the white noise generator is connected directly to the audio amplifier. A problem that occurs with very fast rising stimuli is the onset transient, a ‘‘frequency splatter’’ of sound energy thatmay be more intense, and of wider bandwidth, than the actual stimulus being used (Berg & Balaban, 1999). Therefore, researchers should report whether stimulus onset is uncontrolled or is controlled with an electronic switch, which can reduce some of the frequency splatter.

The duration of the stimulus also affects startle responding. Longer duration stimuli, up to approximately 50 ms, are associated with larger response magnitude and amplitude, and higher response probability (Blumenthal, Avendano, & Berg, 1987; Blumenthal & Berg, 1986b; Putnam & Roth, 1990). This duration

effect has also been found for low-intensity startle stimuli (Blumenthal & Goode, 1991), and reflects the summation of energy in the auditory system (Graham, 1979; Zwislocki, 1969). Based on these results, a 50-ms stimulus duration will typically be sufficient for startle elicitation. Presenting two or more brief startle eliciting stimuli with onsets separated by less than 50 ms can also result in temporal summation, or greater responding than to a single brief stimulus (Blumenthal & Berg, 1986b).

Another factor to consider is the level of noise in the testing environment, which may either mask a prepulse in a startle modification study or act as prepulses (Blumenthal, 1999). Many studies, especially those investigating prepulse inhibition in clinical samples, utilize a steady 65–75 dB background noise during the testing session, whichmasks less intense environmental noise. Background noise at 70–80 dB increases the startle response in rats relative to a ‘‘silent’’ background (Hoffman & Fleshler, 1963), as does background stimulation with 65–85 dB pure tones (Yamasaki & Miyata, 1982). Also, prepulse inhibition in rats is less pronounced in the presence of a 60-dB background noise than a 50-dB background noise (Miyazato, Skinner, & Garcia-Rill, 1999), possibly due to the increase in startle reactivity just mentioned. A parametric test of the impact of background noise that is on throughout the testing session on human acoustic startle has not yet been reported. However, the evidence from both animal and human research suggests that the use of background noise to mask environmental sounds may not be as effective as decreasing those uncontrolled sources of noise or isolating the participant from that environmental noise.

Stimulus creation. Acoustic stimuli can be created by commercially available tone and noise generators or by computer software and sound cards. Software-generated stimulimay allow for more precision of frequency composition and also allow the researcher to anchor pure tone onset to a zero crossing. If software-generated noise stimuli are used, an output frequency of at least 40 kHz is recommended to adequately represent the highfrequency components of the noise stimulus. If the frequency composition of the eliciting stimulus is of interest, the signal being sent to the speaker or headphones can be directed to a data acquisition programwith a high sampling rate (40 kHz), and this sampled signal can then be subjected to Fourier analysis to determine the relative frequency components in the stimulus. Further, the output of the speaker or headphones could be directed to a microphone or sound level meter whose output can be sampled by the data acquisition system, with a Fourier analysis being used to identify the frequencies that are presented to the participant (although the limitations imposed by the microphone must be considered in this instance). By sampling and recording the stimulus output as if it were an input line during data collection, a researcher can be certain of the timing of stimulus onset relative to response onset.

Stimulus presentation. Acoustic startle stimuli can be presented either with loudspeakers or headphones, both of which should have a wide range of frequency and intensity responses. With speakers, calibration of stimulus intensity is accomplished by use of a sound level meter placed at the level of the participant’s head or with the aid of an artificial head or artificial ear. With headphones, the shape of the earphone should allow the fitting of the appropriate adapter of a sound level meter in order to calibrate stimulus intensity. Some sound level meters include settings for the measurement of transient (impulse) signals, although most researchers report the intensity of a steady-state

signal using the dB(A) SPL scale.
The decision of speakers versus headphones depends on a number of factors. In general, it is possible to ensure a more uniformand reliable signal intensity by using headphones as long as the earphones are properly aligned with the auditory canal. Also, calibration of signal intensities is difficult to accomplish as precisely with speakers; this is particularly true when pure tone stimuli are used, due to the occurrence of standing waves. However, speakers may be preferable when headphones might interfere with electrodes, with other sensors mounted on or near the head (e.g., in magnetoencephalogram recordings), or with head-mounted virtual reality displays. There may also be some populations where, due to age, psychopathology, or other factors, the less intrusive nature of speakers makes them preferable.

Visual Stimulation

There are two, apparently unrelated, blink responses to visual stimuli. The effective stimulus for the photic blink reflex is a sudden increase in illumination, whereas the Cartesian blink

reflex (or ‘‘blink to visual threat’’) is triggered in response to a rapidly approaching stimulus. It is unclear whether either of these reflexes is a component of startle; however, the photic blink seems a more likely candidate as it is unlearned and subcortically mediated, whereas the Cartesian blink develops only with experience and requires an intact neocortex (see Hackley & Boelhouwer, 1997). Studies of the photic blink reflex should report the following eliciting stimulus parameters: peak intensity (luminance), duration, rise/fall time, predominant wavelength (if the light is not white), size, and position relative to fixation (in degrees of arc; Hopf, Bier, Breuer, & Scheerer, 1973; Manning & Evinger, 1986), as well as ambient viewing conditions.
When weak, brief, or nonfoveal light flashes are used to elicit the photic blink reflex, two bursts of orbicularis oculi EMG activity can be distinguished (reviewed in Hackley & Boelhouwer, 1997), referred to either as the R50 and R80, to indicate their typical onset latency in milliseconds, or as R2 and R3, to parallel the nomenclature used for the trigeminal blink reflex (see the section ‘‘Electrical, Magnetic, and Mechanical Stimulation’’ below). To avoid contamination of the early EMG component by the electroretinogram (ERG; Hackley & Johnson, 1996), at least one of the following precautions should be taken: (1) Set the low frequency cutoff for EMG recording at 28 Hz to eliminate lower frequency ERG components (van Boxtel, Boelhouwer, & Bos, 1998) and reject blinkswith an apparent onset latency of less than 40 ms, because a high frequency burst of ERG is elicited 10 to 40 ms following stimulus onset. (2) Use a short interelectrode distance, because the retina is farther away from the electrodes than is the orbicularis oculi muscle. (3) Optimally, cover one eye with an opaque plastic eyepatch and record EMG from this occluded eye, because the response is the same on both sides (bilaterally equivalent; Hackley & Johnson, 1996).

Electrical, Magnetic, and Mechanical Stimulation

Blink reflexes can be elicited by stimulation of trigeminal cutaneous nerve fibers with transcutaneous electrical or magnetic stimuli (circumventing cutaneous receptors) or by mechanical stimulation of trigeminal skin areas with discrete taps or airpuffs. Response probability is generally higher with electrical or magnetic stimulation, due to the synchronous firing of afferent nerve fibers. Mechanical stimuli are somewhat less effective because they induce short asynchronous trains of afferent impulses. However, both methods elicit blinks that are more resistant to

habituation than responses to acoustic or visual stimulation.
Electrical and magnetic stimulation. Electrical stimuli are usually applied via two Ag/AgCl electrodes filled with electrolyte gel. Stimulus electrodes should have similar levels of impedance to reduce stimulation artifacts caused by capacitive coupling between stimulation and recording electrode leads (McGill et al., 1982; Merletti, Knaflitz, & De Luca, 1992; for recommendations regarding electrode application see the section ''Skin Preparation'' above). Blink reflexes can be elicited by stimulating cutaneous branches of each of the sensory divisions of the trigeminal nerve (supraorbital, infraorbital, and mental nerve; Gandiglio & Fra, 1967; see Figure 1), although the supraorbital nerve is most commonly used. The cathode is placed over the supraorbital foramen above the eyebrow, where the supraorbital nerve emerges from the skull, and the anode is placed about 2 cm higher and slightly more laterally (see Figure 1). To obtain large and stable reflex responses, electrode contact area diameter should be more than 5mm and interelectrode distance (between the edges of contact areas) should be at least 15–20mm. Small contact areas and interelectrode distances can produce a high local current density, thereby increasing excitation of superficially located nociceptive Aδ fibers, which mediate sensations of pain and temperature, rather than deeper lying Aβ fibers, which mediate touch (Kaube, Katsarava, Kaufer, Diener, & Ellrich, 2000).With larger electrodes that are spaced sufficiently, electrical stimuli within the range of effective blink-eliciting intensities are generally not painful. Nevertheless, application of electrical stimulation may be threatening and the affective consequences of this stimulation method should be considered.

Electrical elicitation of blink reflexes is normally performed using a monophasic rectangular current pulse delivered by an electrically isolated stimulator, with pulse intensity being inversely related to pulse duration for pulses producing threshold excitation (McNeal, 1976). A stimulus duration of 0.1 ms and an intensity between 4 and 8mA is usually adequate to elicit blink reflexes without pain. If necessary, the duration can be prolonged to 0.2 or 0.5 ms. Although the optimal stimulus intensity varies considerably between individuals, it is generally higher than the sensation threshold and lower than the pain threshold (Ellrich, Katsarava, Przywara, & Kaube, 2001).

Stimuli with nonpainful intensities elicit a brief ipsilateral biphasic, triphasic, or polyphasic EMG response with a latency of 9–12 ms (the R1 component), followed by a bilateral polyphasic EMGburst with a latency of 25–35 ms (the R2 component, which is most often reported in startle research). Ipsilateral and contralateral R2 components show decreasing latency and increasing duration with increasing stimulus intensity (Berardelli et al., 1985). Following the R2 component, a bilateral polyphasic component with a latency of 70–90 ms, R3, is sometimes observed. R3 latency decreases with increasing stimulus intensity, resulting in a merging of R3 onset with the tail of R2 (Rossi, Risaliti, & Rossi, 1989). R3 habituates very quickly and is reported to be abolished when the participant pays attention to the stimulus (Rossi et al., 1993).

Magnetic stimulation, inducing an electrical current in the underlying nerve tissue, is an alternative to electric stimulation. Magnetic stimuli are less likely to be painful and, therefore, may be better tolerated. Due to the rapidly growing popularity of transcranial magnetic pulse stimulation (TMS), the technology is readily available. EMG responses elicited in orbicularis oculi by magnetic stimulation of the supraorbital nerve using a small circular coil with an outer diameter of 70mm show strong similarities

with those obtained electrically, an early ipsilateral R1 and a late bilateralR2 (Bischoff, Liscic, Meyer, Machetanz,&Conrad, 1993).

Mechanical stimulation. Blink reflexes can be elicited by discrete taps or airpuffs to skin areas innervated by the trigeminal nerve. These stimuli activate low-threshold mechanoreceptors innervated by nerve fibers in the A_ fiber range (Johansson, Trulsson, Olsson, & Westberg, 1988; Mizobuchi et al., 2000). Mechanical stimulation parameters (intensity, duration, waveform) are generally less effectively controlled than are electrical stimulation parameters. Another problem with mechanical stimuli is the occurrence of acoustic artifacts, via air or bone conduction, that may contribute to the blink reflex response (Flaten &Blumenthal, 1998). However, airpuffs offer a useful alternative in the study of populations with impaired hearing.

The blink reflex can be elicited by a brisk tap on the skin over the lower, medial part of the forehead between the eyebrows (the Guidelines for human startle eyeblink EMG studies 5 glabella) or the supraorbital region (Gandiglio & Fra, 1967; Shahani&Young, 1972). Solenoid and pneumatic devices, which have replaced manual tapping, produce more standardized stimuli (Beise, Kohllo¨ ffel, & Claus, 1999; Hoffman & Stitt, 1980; Snow & Frith, 1989). Mechanical or electrical stimulation of the glabella produces bilateral R1 and R2 responses (Shahani & Young, 1972; Snow & Frith, 1989), whereas lateralized stimulation of the supraorbital skin elicits an ipsilateral R1 response and a bilateral R2 response (Beise et al., 1999; Gandiglio & Fra, 1967; Rossi et al., 1989). Mechanical R3 responses can be found with painful taps to the supraorbital skin (Beise et al., 1999). Similar to the electrically elicited R3, the mechanical R3 habituates quickly and is strongly reduced during attention to the stimulus. The response latencies of mechanical R1, R2, and R3 responses are 6–7ms longer than the latencies following electrical stimulation, reflecting the longer activation times of mechanoreceptors and the less synchronous discharges of the afferent nerve fibers.

Airpuff stimuli directed to the skin anywhere in the upper part of the face elicit blink reflexes as effectively as do electrocutaneous stimuli but, as noted above, may be less anxiogenic. For a description of the stimulation apparatus, see Haerich (1998) or Berg and Balaban (1999). Airpuffs of sufficient intensity elicit R1 and R2 responses with onset latencies longer than those of electrically elicited blinks due to the delay introduced by mechanoreceptor activation time. Airpuff stimuli are very effective when directed to the forehead (e.g., Grillon&Ameli, 1998) or the anterior part of the temporal region between the outer canthus of the eye and the anterior margin of the auditory meatus (e.g., Haerich, 1994; Hawk&Cook, 1997). Spreading of air flow to the cornea should be avoided because this can cause discomfort. The intensity of the airpuff stimulus will vary with air pressure, the diameter of the air tube’s orifice, and the distance from the orifice to the skin. With an orifice of 0.5–1 cm at a distance of 1 cmfromthe skin lateral to the outer canthus, a stimulus with an outflow air pressure in the range of 5–35 kPa is usually sufficient to elicit a robust blink reflex (Berg & Balaban, 1999; Haerich, 1998; Hawk & Cook, 1997). Stimulus duration is usually in the range of 100–300 ms. Airpuffs regulated by solenoid-operated valves (Haerich, 1998) may have slow rise and fall times, which cause uncertainty about the temporal relationship between the stimulus and the activation of cutaneous receptors. A high-speed air control system that delivers brief airpuffs (duration 1.2 ms, rise time 0.5 ms) with high peak pressures (maximally 122 kPa) to

small areas of skin (2.5mm2) avoids this (Hashimoto, 1987; Mizobuchi et al., 2000). Stimulus duration, rise time, and transmission time should be reported by recording the output of a microphone positioned at the orifice of the air tube.

Electrical noise and clicks produced by a solenoid-operated valve can be avoided by shielding and insulating the valve or by placing the equipment in a separate room. The flow of air itself causes an acoustic artifact via air or bone conduction (Flaten & Blumenthal, 1998; Haerich, 1998), which summates with the tactile stimulation and may contribute to the blink reflex. The acoustic component can be masked by presenting background noise through the headphones (Miller, Curtin, & Patrick, 1999), although the possible impact of this noise on startle reactivity must be considered (see the section ''Stimulus Properties'' above). Alternatives include the use of sound-attenuating headphones or earplugs or lowering the intensity of the airpuff (such as by using tubing with a smaller internal diameter; Flaten & Blumenthal, 1998; Haerich, 1998). The intensity and temporal characteristics of the acoustic stimulus component should be measured and reported.

Amplification, Filtering, and Integration of the EMG Signal

Like all EMG measures, eyeblink EMG is measured as a relatively high-frequency signal that oscillates in positive and negative directions around a zero-voltage level (Figure 2). The conditioning of this signal may include various combinations of analog and digital operations (Figure 3). The raw EMG must first be amplified. Second, the signal is filtered to minimize noise

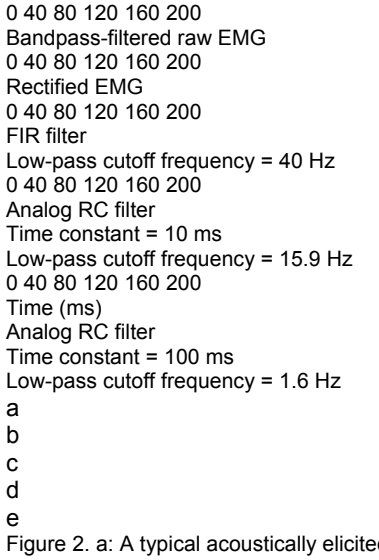

Figure 2. a: A typical acoustically elicited eyeblink EMG response that was digitally filtered (28–500 Hz passband) and sampled at 1000 Hz.The eliciting stimulus (presented at 0 ms) was a 95 dB(A), 50 ms duration broadband noise burst with a rise/fall time shorter than 1 ms, presented via headphones (AKG, Model K100). In (b), EMG was rectified. This signalwas then smoothed, eitherwith (c) a variable-weight FIRfilter (101 coefficients, low-pass cutoff frequency 40 Hz), or (d and e) a digital implementation of an analog resistor-capacitor (RC) filter (time constant 10 ms or 100 ms).

that is above and below the EMG signal frequency band. Third, because the negative and positive components of the waveform could cancel each other out in subsequent processing, the signal is rectified (conversion of data points into absolute values). Finally, the signal is either integrated or smoothed. The following sections provide guidelines for each of these steps.

Amplification

The eyeblink EMG signal is differentially amplified, preferably with an isolated AC-amplifier with a high input impedance (4100MO), high common-mode rejection ratio (4100 dB), and low input noise (*o*1 *m*V RMS in the frequency range of 10–500 Hz). Because of the large dynamic variations in blink EMG response amplitude across participants, stimulus conditions, and trials, the amplification factor demands special attention. Too much amplification can cause the signal to exceed the input voltage range of the analog-to-digital (A/D) converter (signal clipping). Too little amplification can result in an inability to detect small responses, particularly when A/D converter resolution is low (e.g., 256 or 4096 digital units associated with an 8-bit and 12-bit converter, respectively). The range of amplification can be explored by eliciting a few blink reflexes prior to the experimental session, if this is not incompatible with the research paradigm. However, these problems can be avoided by using a high-resolution A/D converter (16 or 24 bits), whichwill preserve sufficient resolution even when only a limited portion of the input voltage range is utilized. Another advantage of high-resolution A/D conversion is that the need for manual gain adjustment for each recording channel and participant is eliminated, as is the subsequent calculation required to correct for such changes during data scoring and analysis.

Filtering

Following amplification, the EMGsignalmust be conditioned to maximize the signal-to-noise ratio, thereby increasing the fidelity with which the actual blink response is discriminated from the background. Although a tutorial on filtering (e.g., Cook & Miller, 1992) is beyond the scope of this article, a few definitions are provided here.Ahigh-pass filter removes frequencies belowsome designated cutoff frequency, whereas a low-pass filter removes frequencies that are higher than the cutoff frequency. Input frequencies beyond the cutoff frequency are not completely eliminated from the output. Rather, the further the input signal frequency is beyond the cutoff frequency, the more the output signal is attenuated. The steepness of this ‘‘rolloff’’ function depends on the filter design, and is generally specified in dB per octave (where an octave is the doubling or halving of the cutoff frequency). The passband refers to the range of frequencies that a filter will pass without substantial attenuation, the stopband is the range of frequencies in which little energy is passed, and the transition band is the range of frequencies in which gain is intermediate. A variety of signal conditioning procedures may be used, consisting of analog and digital operations (Figure 3). Within each procedure, the eyeblink EMG signal is high-pass filtered to remove low-frequency artifacts (e.g., motion artifacts and

Guidelines for human startle eyeblink EMG studies 7

Analog integration
Analog smoothing
Alternative 1
AC amplification
AC amplification
AC amplification
AC amplification
AC amplification
Alternative 2 Alternative 3 Alternative 4 Alternative 6
Analog lowand

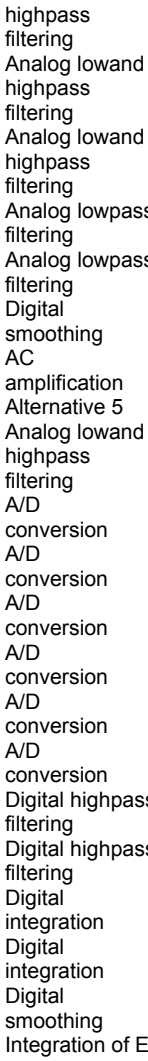

Figure 3. Different procedures for analog and digital processing of the eyeblink EMG response signal. Analog or digital smoothing consists of rectification and low-pass filtering of the EMG signal.

potentials from other biological sources), and low-pass filtered to reduce wide-band noise (e.g., instrumentation noise, electrode–skin noise) and to remove specific high-frequency components caused by electromagnetic interference (e.g., radio waves, harmonics of the power line frequency). Adequate low-pass filtering also prevents aliasing of digitized signals (see the section ‘‘Analog-to-Digital Conversion’’ below).

The EMG signal may be contaminated by low-frequency potentials from different sources, the most important of which are motion potentials associated with the contraction of orbicularis oculi. These potentials are largely caused by stretching of the skin under the electrode, causing changes in the potential between the electrolyte gel and the skin (O¨ dman &O¨ berg, 1982). Eyeblink EMG responses can also be affected by other lowfrequency artifacts, such as those generated by eye movements, overlapping electrode collars, retinal potentials, and activity of other facial muscles. Low-frequency artifacts can be minimized by high-pass filtering of the EMG signal, with a cutoff frequency high enough to achieve adequate artifact removal but not so high that a substantial portion of the EMG signal is filtered out. This point is particularly important in research paradigms in which

small blink responses may occur, such as after response habituation.
Using a digital high-pass filter with an infinite impulse response (4th order Butterworth filter, rolloff 24 dB per octave), van Boxtel et al. (1998) determined that adequate artifact rejection, while preserving real EMG signal components, could be accomplished by a filter with a _3 dB cutoff frequency of 28 Hz (Figure 4). This frequency was found to be optimal for acoustic, photic, and electrocutaneous blink reflexes recorded with varying interelectrode distance (12 and 36 mm, center-to-center). The 28-Hz high-pass cutoff frequency should be considered as an approximate guideline rather than as an absolute standard, because the cutoff frequencies investigated were incremented in steps of 8 Hz, implying that the optimal frequencymight actually reflect a value in the range of 24–32 Hz. Also, when using a filter with a rolloff of less than 24 dB per octave, the cutoff frequency should be higher than the recommended frequency and, conversely, the cutoff frequency can be lower with a rolloff of more than 24 dB per octave.

Low-pass filtering reduces high-frequency components caused by instrumentation noise and electromagnetic interference (e.g., radio waves, harmonics of the power line frequency). For all stimulus modality and interelectrode distance conditions, van Boxtel et al. (1998) found that a low-pass cutoff frequency of 400–500 Hz appeared to be adequate because there was a negligible contribution of higher frequency components to the EMG signal (Figure 4). In general, a low-pass filter with a steep rolloff (24 dB per octave or greater) is recommended for EMG signals (Clancy, Morin, & Merletti, 2002). Adequate low-pass filtering also prevents aliasing of digitized signals (see the section ‘‘Analog-to-Digital Conversion’’ below).

Although high-pass filtering is necessary for reliable measurement of the acoustic blink reflex and its electrocutaneous and visual counterparts, it may cause problems when measuring the magnitude of the biphasic or triphasic electrocutaneous R1 component. The R1 component may be contaminated by the response of the high-pass filter to the electrical stimulation artifact shortly preceding R1. Apart from taking measures to reduce stimulation artifacts (McGill et al., 1982; Merletti et al., 1992), van Boxtel et al. (1998) recommend measuring R1 amplitude using a parallel recording of the EMG signal on a separate channel with a lower high-pass cutoff frequency (e.g., 0.5 or 1 Hz).

The blink reflex EMG signal may be high-pass filtered online, using an analog filter (Figure 3, alternatives 1, 2, 4, and 5), or off-line, using a digital filter (Figure 3, alternatives 3 and 6). Digital filtering can also be performed on-line if computer processing capacity is sufficient. The primary advantage of digital filters is that they show no limitation in settings and may be repeatedly applied off-line to stored EMG data with modified settings, whereas analog filtering is usually associated with limited settings and irreversible results. In any case, storage of the minimally filteredEMGdata is recommended so that the original signal can be filtered digitally in a different way at a later time, if the need arises. Another advantage of digital filters is that they can be exactly specified and are completely consistent in their operations, whereas analog filters do not always conformto their specifications and may show some variability at different times or across different recording channels. Therefore, analog filters need to be calibrated periodically to ascertain that their characteristics have not changed. Finally, a narrow transition band (a steep rolloff) can be more easily obtained with digital filters than with commonly available analog filters (Cook & Miller, 1992;

Nitschke, Miller, & Cook, 1998).
A disadvantage of analog filters and digital infinite impulse response (IIR) filters is that they may introduce frequency-dependent phase shifts in the EMG signal, which can result in increased response onset latency and distortion of the input waveform. Symmetrical digital finite impulse response (FIR) filters do not cause phase shifts. Phase shifts and the accompanying increased latencies are less problematic in within-participants designs because they are consistent across experimental conditions (under the reasonable assumption that the frequency characteristics of the EMG signal do not change). If distortion of the signal waveform would be problematic, an analog filter with linear phase shift (a Bessel type filter), which does induce a time shift but produces minimum signal distortion, can be applied.

Rectification and Integration or Smoothing

The next stage of processing involves rectification and integration or smoothing of the signal (Figure 2). Rectification (conversion to absolute values) can be accomplished either with an analog circuit designed for this purpose or digitally. In either case, it is necessary to check whether the output DC level of the

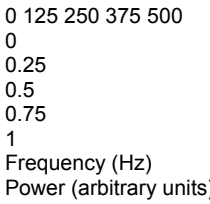

Figure 4. Typical power spectra of acoustically elicited eyeblink EMG responses in three different persons. EMG was digitally filtered (28–500 Hz passband). A data record of 128 ms duration, starting at acoustic stimulus onset, was sampled at 1000 Hz, tapered by means of a Kaiser-Bessel window, and subjected to power spectral analysis.

amplifier is centered on zero; if it is not, the usual procedure is to subtract the average unrectified signal amplitude calculated for a prestimulus baseline period from each data point of the rectified poststimulus signal.

Conditioning of the EMG signal may be completed by integration or smoothing. Real (i.e., mathematical) integration involves computing the area under the curve of the EMG signal during a certain time interval (Herzog, Guimaraes, & Zhang, 1999). The outcome, expressed in microvolt _ seconds, is related to the tension or force exerted by the muscle (De Luca, 1997; Winter, 1990). Integration can be performed with an analog device (Figure 3, alternative 1) or a digital routine (Figure 3, alternatives 2 and 3). Analog integrators deliver a signal proportional to the value of the integral during an internally or externally controlled time interval; this signal is typically digitized prior to data quantification. However, integration is most often performed using a digital routine, wherein the digitally calculated integral (or response area) is the product of the mean rectified voltage during the integration interval and the duration of the interval.

A more common procedure, as illustrated in Figure 3 (alternatives 4–6), is smoothing of the EMG signal (Winter, 1990), which involves passing the rectified EMG signal to a low-pass filter. This can be performed on-line using an analog device (Figure 3, alternative 4) or off-line using a digital routine (alternatives 5 and 6). Such an analog device, consisting of a precision rectifier and a low-pass filter, is often called a ‘‘contour-following integrator’’ (e.g., Fridlund, 1979), so that the term ‘‘integration’’ has often been used in the literature when ‘‘smoothing’’ would have been more accurate. The low-pass filter usually consists of a

simple resistor-capacitor (RC) circuit. The _3 dB cutoff frequency (f_c) of such a filter can be derived from its time constant (t, in seconds): $f_c = 1/(2\pi t)$, with higher time constants representing lower cutoff frequencies. As illustrated in Figure 2d,e, increasing the time constant reduces the impact of high frequency fluctuations in the rectified EMGsignal (both during the baseline period and the blink response). However, increasing the time constant also leads to attenuation of the output signal relative to the input signal (Blumenthal, 1994, 1998). At long time constants, this may result in a failure to detect small responses, potentially overestimating the proportion of participants with subthreshold blink responses (''nonresponders''). Blumenthal (1994) found that using a time constant longer than 10 ms decreases the probability that small or brief responses will be detected.

As with analog filters used to condition the raw EMG signal, the low-pass RC filtermay introduce frequency-dependent phase shifts, as in Figure 2e. This problem can be avoided by using an analog Bessel filter rather than a simple RC filter. A higher order Bessel filter would also provide a much steeper rolloff, and would, therefore, better suppress random fluctuations in the rectified EMG signal.

Smoothing of the EMGsignal can also be performed digitally (Figure 3, alternatives 5 and 6). An IIR filter that acts as an RC circuit (Bendat & Piersol, 2000, p. 401), or simulates other types of analog filters, may be used. Also, a variety of symmetrical FIR filters (preventing phase shifts) can be implemented. A commonly used FIR filter for smoothing is the moving average, or boxcar, filter. In fact, this fixed-weight filter attenuates all frequency components in the EMG signal except 0 Hz.The primary advantages of this filter are its simplicity and speed of computation, although it has several limitations that can be avoided by using a more sophisticated variable-weight FIR filter (Nitschke et al., 1998). This type of filter, illustrated in Figure 2c, has several advantages in comparison with analog RC filters. Besides avoiding phase shifts, it also avoids the multiple peaks as observed in the output of RC filters with a short time constant, as well as the strongly attenuated output of RC filters with a long time constant.

Analog-to-Digital Conversion

The sampling rate for analog-to-digital (A/D) conversion of raw or smoothedEMG depends on the highest frequency component of interest in the signal, and should be sufficiently high to enable unique reconstruction of the original signal. Because at least two samples per sine wave cycle are needed for reconstruction of both phase and amplitude, the highest frequency component in the original signal that can be detected is half the sampling rate. This frequency component is called the Nyquist frequency or folding frequency. Frequency components in the original signal above the folding frequency will not be lost from the signal, but will be folded back into the frequency range from the folding frequency down to 0Hz (a process called aliasing; Bendat & Piersol, 2000, pp. 366–369). This implies that high signal frequencies that are not of interest, and thatmay be artifacts rather than actual EMG components, can contaminate the real EMG signal. Therefore, it is recommended that the frequency range of the original analog data be restricted with an analog low-pass filter prior to A/D conversion (Figure 3) so that frequencies beyond the highest relevant signal frequency are removed (anti-aliasing filtering). An analog filter is suggested because, once the signal is digitized, the contaminating effects of aliasing are irreversible. Because no analog filter has an infinitely steep rolloff, it is customary to set the

anti-aliasing filter cutoff frequency at a lower value than the folding frequency, depending on the rolloff of the filter (Bendat& Piersol, 2000, pp. 368–369). Low-pass filtering with a cutoff frequency within the range of 400–500 Hz to prevent aliasing is adequate for raw EMG signals (van Boxtel et al., 1998), if sampling rate is 1000 Hz or more. Sampling the analog smoothed EMG (Figure 3, alternative 4) requires a much lower sampling rate because the high-frequency components are already removed from the signal. Nevertheless, a higher sampling rate might be necessary for the precise determination of response onset latency and peak latency. For this reason, we recommend that both the raw and the smoothed EMG signal be sampled at a rate of at least 1000 Hz.

Measurement Units

As indicated above, integrated blink EMG magnitude is expressed inmicrovolt _ seconds, whereas the peak amplitude of the smoothed EMG response is expressed in microvolts. Eyeblink EMG amplitude (or magnitude) has in the past often been reported in analog-to-digital units, or arbitrary units, neither of which can be directly compared across research settings. Conversion to microvolts or, in the case of integrated EMG, microvolt _ seconds, would facilitate comparisons across experiments and laboratories. This is the norm in all other branches of electrophysiological research and adoption of this standard by startle researchers is recommended.

Comparability across research settings would also be facilitated by reporting the details of a microvolt-level calibration procedure. Specifically, a calibration signal can be generated by the computer's digital-to-analog converter or other equipment for transmission to the coupler or preamplifier of the EMG Guidelines for human startle eyeblink EMG studies 9 recording system. (Some differential bioamplifiers may not operate properly when the input is a single-ended output from a D/A converter. In this case, the D/A output may need to be routed to the next stage in the processing sequence, which will typically be single ended rather than differential.) Using this procedure, the impact of data processing can be quantified by comparing the original calibration signal to the resulting signal after amplification, filtering, smoothing, and so forth. These calibration procedures and the ratio of output to input could be reported along with the experimental data, allowing startle researchers to compare their own results with results from other research laboratories.

Because response measures can be influenced by the decisions made regarding recording and calibration methodology, investigators are encouraged to report relevant aspects ofEMG signal processing, including cutoff frequencies and rolloffs for analog and digital filters, integration parameters or smoothing coefficients, A/D converter resolution (bits), and sampling rates.

Quantifying the Startle Blink EMG Response

Response Quantification

Response quantification involves identifying and measuring EMG parameters such as onset latency and peak amplitude (Berg & Balaban, 1999). During the scoring process, startle blink responses must be distinguished from background EMG activity and from voluntary and spontaneous blinks. The inclusion of these other blinks can be minimized by limiting acceptable reflex responses to blinks with response onset in a narrow latency window following eliciting-stimulus onset. Common response onset latency windows include 21–120 ms for acoustically elicited blinks (suggested by Balaban, Losito, Simons, & Graham, 1986) and 21–150 ms for visually elicited blinks (Graham, 1975).

However, these values were based on norms for a very wide age range. The relatively low standard error of onset latency measurement (e.g., Blumenthal, Elden, & Flaten, 2004) suggests that a narrower window (e.g., 21–80 ms) might be more appropriate for adult acoustic startle experiments, particularly when a short EMG smoothing time constant is used.

The nature of the EMG waveform being quantified has a significant impact on the startle parameters that will be obtained. For example, long smoothing time constants produce a significant reduction in indices of response size (amplitude, magnitude, area). Similarly, indices of response speed (onset latency, peak latency, response duration) are most accurately obtained from the raw EMG waveform(e.g., Blumenthal, 1994, 1998). Because the time constant of EMG integration (or the degree of smoothing of the signal) can delay the peak, measures of peak latency should be interpreted with caution.

Data scoring can be donemanually orwith computer-assisted scoring or with fully automated procedures, and each method is based on user-defined scoring parameters. Manual scoring involves the scorer's selection of response onset, peak, and so forth, on a trial-by-trial basis. With computer-assisted scoring, the program identifies response parameters based on user-defined criteria, but each response is visually inspected and an acceptance or override decision is made. In the case of either manual or computer-assisted scoring, the procedure should be done blindly with respect to experimental condition, the parameter identification and measurement rules should be reported, and, ideally, interrater reliabilities for subjective aspects of these procedures should be documented. For reasons of speed, cost, and consistency, some investigators prefer fully automated systems. However, visual inspection allows a researcher to accept or reject trials based on his or her seasoned judgment. Whatever criteria or methods are used to score EMG data, these should be applied in a consistent manner across data sets and across data scorers. If more than one person scores the data from a study, interscorer reliability should be maximized by adequate training in the scoring methods used.

For each trial, the researcher or scoring program must first decide whether a response could have been seen had one occurred. If the baseline period is contaminated with noise, movement artifact, and so on, or if a spontaneous or voluntary blink begins before the minimal onset latency value, then a stimuluselicited blink cannot be accurately quantified on that trial. Thus, the trial should be rejected. On trials that are not rejected, the next decision is whether or not the criterion for response onset has been met. If not, then this trial represents a failure of the stimulus to elicit a response, that is to say, a nonresponse trial (also called a ''flat response'' or a ''zero response'').

Identification of the onset of a blink response can involve searching forward in the EMG waveform from the time of stimulus onset for a significant increase or change in slope of the waveform or, alternatively, searching backward from the peak of the response to this initial point of change (although thismethod assumes that a response is seen on this trial). Because there is always noise in the EMG signal, the change in slope can be thought of as a change in slope of the line of best fit, which can be established statistically or by visual estimation. A variety of response onset criteria have been used in previous research, such as the first point that is two standard deviations above the baseline mean (Ornitz, Hanna, & de Traversay, 1992); or the first point that is at least three times the mean of the baseline (Grillon & Davis, 1995) or the first point at which the slope of the EMG

signal changes by some number ofmicrovolts (or arbitrary units) within some number of milliseconds (or samples; Blumenthal, 1995; Hamm, Greenwald, Bradley, & Lang, 1993; Vrana, 1995). All of these require that the EMG signal exceed the baseline EMG activity by some factor. The optimal method of onset latency determination is still an open question (Brinkworth & Turker, 2003; Leader, Boston, & Moore, 1998; van Boxtel, Geraats, van den Berg-Lenssen, & Brunia, 1993).

Similar to the procedure for determining response onset, identifying the peak of a startle blink response involves examination of the EMG waveform within a particular time window (e.g., from 20 to 150 ms after stimulus onset for acoustic blinks). The most common method for determining response peak is to simply identify the maximal EMG value within this specified window. If multiple peaks occur, as is often the case when short smoothing time constants are used, the maximum value is still identified as the peak, unless the EMGresponse line has returned to baseline for a long enough time that the later peaks are clearly not components of the stimulus-elicited response. The definition of these criteria is still an open question, and the researcher should report whatever decision is made regarding multiple peaks. The minimum acceptable response size (response criterion) should also be reported. Note that a criterion that is too low can result in nonresponses being scored as responses, whereas too high a setting can cause ‘‘true’’ blinks to be missed and scored as nonresponses.

With the onset and peak of a response determined, indices of response size can be computed. Response amplitude is typically

computed as the difference between the EMG value at response peak and either the EMG value at response onset or the average EMG value during a baseline period preceding or immediately following eliciting-stimulus onset. This baseline period should, of course, end before the beginning of the response onset window. Once response amplitude has been computed for each trial, two options for averaging across trials include computation of mean response amplitude and probability or combining these into mean response magnitude. The terms amplitude and magnitude are interchangeable when describing the size of a single response, but they differ when describing the average across trials. In that case, the term magnitude is traditionally used when the average includes values of zero for nonresponse trials, whereas the term amplitude is used if the average is computed with nonresponse trials excluded. Response probability refers to the total number of detected responses divided by the total number of eliciting stimuli presented (after adjusting for trials contaminated by artifact), within each stimulus condition. The mean response magnitude for a set of trials is the product of the mean amplitude within that condition and probability for that condition (mM5mA _ P; Blumenthal & Berg, 1986a). This implies that, as response probability increases,mean response magnitude approaches mean response amplitude. The term magnitude should be used, rather than amplitude, to describe the size of signal averaged EMG (see the section ‘‘Signal Averaging versus Analysis of Single Trials’’ below), because trials with no response are normally included in the computation of these averaged waveforms.

The startle blink parameters described thus far are computed using two data points in the EMG signal, response onset and peak. Response peak may provide information about the activation of the largest motor unit in close proximity to the electrodes, although it could be based on the simultaneous activity of

several smaller motor units. To examine the activity of all recruitedmotor units, measures of response duration and areamay be computed using the points of response onset and recovery to baseline. Response duration is defined as the time from response onset to response recovery and reflects the duration of agonist muscle activation during the blink response. Response area is defined as the area under the curve of a response waveform and reflects the entire muscle activation. Blumenthal (1998) reported high correlations between measures of response magnitude and response area, using data derived both from raw EMG and from rectified and smoothed EMG. However, it is better to measure response area and duration from raw, rather than smoothed, EMG, because the tail of the smoothed response reflects, in part, the recovery of the smoothing process.

One final step of processing is frequently performed before blink data are subjected to statistical analyses. For reasons as yet largely unknown, wide individual differences in absolute blink magnitude are observed, and this variation is often unrelated to the experimental phenomena of interest. Accordingly, the use of absolute blink magnitudes can result in a small number of subjects with unusually large blinks disproportionately affecting the outcome. For this reason, many experimenters standardize blink magnitudes in some way, such as using all blinks for a given subject as the reference distribution and reporting the results as z or T (mean550, SD510) scores. An alternative is to use only blinks obtained during intertrial intervals, or other nontask parts of the session (control blinks), as the reference distribution (e.g., Bonnet, Bradley, Lang, & Requin, 1995). In this manner, the extent of blink modulation due to the experimental conditions can vary freely in relation to the reference, because they are not part of this distribution's variance. However, this method relies on a sufficient number of control blinks obtained throughout the course of the session (to represent habituation effects adequately) to form a valid reference distribution. An alternative approach is to eliminate participants or individual trials that are considered outliers (e.g., 3 SDs from the mean). Although no preferred method for standardization or rejection of outliers has emerged, any such data transformation should be reported in detail. (The reader is referred to Blumenthal et al., 2004, who discuss similar issues in the context of quantification of prepulsemodification of the blink response.)

Signal Averaging versus Analysis of Single Trials

As discussed above, themost commonmethod of analyzing blink EMG data is to measure the amplitude, onset latency, and probability in single trials, and then calculate the condition means for use in inferential statistics. An alternative approach is to signal average across trials within a condition, measure the resulting waveforms, and then submit these measurements to statistical analysis. The latter technique is identical to that used to extract event-related potentials from EEG, except that EMG signals must be rectified prior to signal averaging. Rectification is necessary because, at any given point in time following stimulus onset, the EMG electrodes are as likely to record a positive as a negative spike, and the sign of the wavelet is generally not an important consideration in differential recording (Melkonian, Blumenthal, & Meares, 2003). If unrectified data were averaged across trials, the positive and negative spikes would cancel out, resulting in a more-or-less flat waveform.

Signal averaging is necessary for the extraction of event-related potentials from EEG because these potentials are smaller than the background activity. This is not the case for EMG blink responses, where the signal is usually considerably larger than the

noise. However, there are several advantages to signal averaging of (unsmoothed) EMG: (1) It allows components of the response (e.g., the R50 and R80 components of the photic blink reflex) to be readily distinguished. (2) Differential effects on these components, or on portions of a single component, can be distinguished in the signal averaged waveforms. For example, prepulse inhibition reduces the amplitude of the peak and trailing edge of the photic R50 component but has no effect on the leading edge of that component (Burke & Hackley, 1997). (3) Signal averaging permits responses that are smaller than the background activity to be detected, provided that these small responses do not vary too much in onset latency. (4) The silent period that commonly follows large EMG bursts can be investigated. (5) Event-related potential or event-related desynchronization data can be collected and analyzed concurrently with startle, to maximize comparability across measures.

The principle disadvantages of signal averaging compared to conventional single-trial analyses are: (1) Stochastic versus amplitude-modulation effects cannot be distinguished. For example, analysis of signal averaged data cannot reveal whether prepulse inhibition produces a reduction in response probability, a reduction in response amplitude, or both. (2) Signal averaging introduces a bias such that the response onset latencies more strongly reflect minima than means. The point of response onset in an averaged waveform, for example, would be primarily determined by the fastest responses of the fastest participants. To reduce or eliminate this bias, the point at which the leading edge of the response first reaches 50% of peak amplitude can be Guidelines for human startle eyeblink EMG studies 11 substituted for response onset latency (Smulders, 1993). (3) Significant variations in the onset latency of responses result in a phenomenon known as ‘‘latency jitter,’’ in which the averaged response peak is lower than any individual peak because the individual peaks occur at different points in time, compromising measures of response magnitude.

If signal averaging is employed, the investigator should report the analog-to-digital conversion rate (in hertz), the type of epoch segmentation (i.e., stimulus- vs. response-locked), the length of the epoch (in milliseconds), and artifact rejection criteria (e.g., blink in progress at the time of stimulus delivery).Waveforms for contrasting conditions should be overlaid in the figures, but no more than four conditions should be superimposed, in the interest of clarity. Time and amplitude scales should be indicated in the figure itself (e.g., with calibration bars) rather than in the caption.

Rejection of Trials and Participants

Because the orbicularis oculi reaches very low levels of noise at rest, the signal-to-noise ratio for startle is generally very high, and what little noise does exist can be reduced considerably by proper skin preparation and electrode placement. In addition to video monitoring of the participant, recording complimentary channels of physiological information such as vEOG, ECG, EEG, and EMG from other pericranialmuscles can be useful for identifying artifacts due to motion or other sources. However, spontaneous blinks should also be considered artifacts when reflex blinks are the response of interest. Gehricke et al. (2002) suggest that reflexive and nonreflexive blinks can be distinguished by simultaneous recording (coregistration) of EMG and vEOG. However, because vEOG is also sensitive to movements of the eyeball, it is not possible to distinguish EOG activity caused by lid movement from that caused by eyeball rotation. The alternative to coregistration is adherence to strict latency

criteria for response onset, with the realization that a narrow window of acceptable onset latencies will decrease the probability of artifact being mistaken for true responding.

The most common procedure for reducing the impact of artifacts on the data is to exclude any trial inwhich there is excessive noise in the EMG signal, or in which a spontaneous blink occurs either in the period immediately preceding stimulus onset or in the interval between stimulus onset and the minimal blink onset latency. Optimal criteria for rejecting a trial will vary depending on the nature of the waveform and the quality of the recording. Regardless of the strategy adopted, the criteria for trial exclusion and percentage of trials lost using these criteria should be reported. Finally, a rejected trial should not be considered equivalent to a trial on which there is no response.

Participants as well as trials sometimes must be rejected, often because the individual exhibited blink responses on too few trials (i.e., a floor effect), or none at all. Such participants are typically labeled ‘‘nonresponders’’ and are excluded from experimental analyses. Attrition rates are typically higher for studies using acoustic and visual eliciting stimuli than for those using electrocutaneous or mechanical reflexogenic stimuli. The problem also increases as stimulus intensity decreases. An informal survey of current practices (C. Patrick, pers. comm.) indicates acoustic nonresponder rates of approximately 5–10% for healthy young adult participants, whereas rates reported for clinical populations, children, and the elderly are somewhat higher. Participants may also be rejected for other reasons, including a restricted range of responding within a specific experimental condition or outlier status based on extreme amplitude or latency values for a given experimental condition. However, the nonresponder category should be used exclusively for participants who fail to exhibit a sufficient number of reflexive responses. The criteria for defining a participant as a nonresponder should be clearly stated, including the minimum number of responses required for inclusion in the study and the response criterion (minimum response detectable with the measurement system used).

Because nonresponding and artifacts can produce a substantial loss of data, it is essential that the experimental design include several trials per condition. Inclusion of ‘‘control trials’’ (e.g., in a prepulse modification study, trials with only a startle stimulus) across the experimental session can provide a gauge of response habituation over trials. The order of stimulus conditions also needs to be counterbalanced to accommodate reduced responding across the session due to habituation. This can be accomplished by presenting blocks of trials, with each block containing one or two trials in each stimulus condition, in counterbalanced or randomized order. The control trials in each block can be used to quantify habituation across the session. In addition, two to four blink-inducing stimuli are often presented at the beginning of the session (in advance of any experimental procedures), with these trials excluded from analysis. These initial blinks are often exaggerated in size, after which habituation follows a more gradual course.

Missing data result in empty cells, and these empty cells are more likely for measures of response amplitude and latency, for which zero is not an acceptable value, than for measures of response magnitude or probability, for which zero is a possible value. Magnitude and probability will be missing only when a trial is contaminated by artifact; amplitude and latency will be missing under these conditions, but also when a response could have been seen but none occurred. This problem becomes more pertinent as the probability of a response decreases, such as when

lower intensity stimuli are used, or after the response habituates or when a prepulse inhibits the startle response. Empty cells cause most ANOVA programs to delete the entire subject, decreasing the N and, thereby, the power of the analysis. These reduced Ns should be reported for each analysis.

When a given trial is determined tomeet criteria for rejection, the investigator must then decide whether to exclude that trial from calculations of the mean in that condition or to select a replacement value.Missing data can be estimated based on valid responses, either of the participant in question (e.g., the average of the preceding and following trials in the same condition or the mean for that subject for that condition) or based on the mean across subjects for that condition. Such an approach is appropriate if the estimates are performed conservatively (i.e., if there is a bias, it would tend to favor the null hypothesis). However, it is often preferable to reject the data of a participant rather than to attempt statistical salvage operations. In either case, the strategy selected to deal with rejected trials should be clearly described.

Conclusions

The present article makes recommendations about specific aspects of startle blink research, illustrating the different outcomes that result from making different decisions on a particular methodological issue. It is acknowledged that decisions about methodology may be constrained by limitations imposed by the equipment used in a particular research setting, and that chang-

ing methodology may limit the extent to which data collected before and after the change can be compared. However, a researcher setting up a new laboratory ormodifying an existing one should consider recording data in as raw a fashion as possible, and then manipulate those data with software rather than hardware, to circumvent some of these equipment-imposed limitations. Independent of the decisions made regarding methodology, it is our recommendation that relevant procedures be fully described in a published report, to assist the reader in evaluating the methodology.

Startle is a sensitive measure that can provide a wealth of information across species and ages, in a variety of areas in the broadly defined fields of psychophysiology and neuroscience. Improving the methodological rigor with which startle data are gathered, analyzed, and reportedwill enhance the interpretability of these studies, increasing the potential contribution of research using this measure. We hope that the guidelines offered in this article will help to decrease the error variability of startle blink data, thereby decreasing noise and increasing precision in the use of this measure in research and clinical applications.

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V85-05C AUDIO SOURCE MODULE

The V85-05C is very nearly a complete audio lab in one module. This dual-channel module has a tone source and
a white noise source with these signal synthesis and control features:

- Manual and programmed control of tone frequency and amplitude.
- Manual control of noise amplitude.
- Programmable dB attenuation of tone, noise and external signals.
- Shaped-rise gating of tone, noise and external signals.
- Shaped attenuation-level transitions of tone, noise and external signals.
- Shaped frequency transitions of tone.
- Mixing of tone, noise and external signals.

Tone frequency may be set manually or by analog program control. The analog signal that controls frequency
may be generated by computer using a D/A converter output, or by another module's analog output.
Changing from one frequency to another frequency using the D/A converter in a "step" fashion will not produce a
"transition click" because the change is shaped by integration (0.1 sec.). Using another module's output as the
controlling source permits frequency modulation of the signal within the limits of this shaping time constant (see
specifications) therefore frequency modulation above 10 Hz is not possible.
When using another module's output to modulate, for example an integrator, where the input signal is a
biopotential, using the contour following output to modulate frequency generates a proportional frequency audio
stimulus for biofeedback.
Tone amplitude may also be set manually or externally controlled in a similar manner. The input may be
controlled by a D/A converter or another module. Amplitude modulated stimuli may thus be synthesized. Because
there is no shaping here, no limitation is imposed as upon frequency modulation (noted above).
Like tone amplitude, noise amplitude may be manually set but it may not be programmed or amplitude modulated
at the source.
Tone, noise and external signals may be attenuated by a pair of independent, programmable attenuators. The
attenuators offer shaped transitions from level to level and may also be used for modulation within the shaping
time constant limitations.
The noise channel may be broken and another signal inserted beyond the source but ahead of the attenuator,
shaped-rise gate and mixer, at the jack labeled "EXTernal SIGNAL". This permits a second tone from another
V85-05C module, or a signal from any other audio source to be introduced. The external signal may then be
passed through the attenuator associated with the noise source, then independently gated and mixed with the
tone from this module. Yet another signal may be introduced after the attenuators at the input marked "EXTernal
SIGnal" and mixed with the two attenuator's outputs.
The signals are then available separately and mixed as audio-industry-standard "line" outputs on the side panel

for connection to a power amplifier. The same signals are available on the rear panel at LabLinc standard levels.

SETTING TONE FREQUENCY

The block of four digit switches is used to either manually set the tone frequency, or to set the range of frequency
as a function of the analog control signal amplitude. The push buttons above each digit increment by one when
79
pressed, and the buttons below decrement by one. The switch to the right is a multiplier function. In the "C"
position, the frequency will be the number set on the 4-digit switch bank. It will be 0.01 times in the "A" position,
0.1 times in "B", and 10 times in "D". Position "P" allows range to be program controlled by the two binary rangecontrol
jacks to the left of the box labeled "Tone Source" on the rear panel.
When a lead is inserted in the jack on the back labeled "PROGram FREQuency", the function of the switch block
is automatically redefined and no longer controls frequency directly. Rather, frequency is now controlled by the
analog level (voltage) on the control lead. The digit switches now control the ratio or amount of control that the
control voltage has over frequency. The manual settings now control how many Hertz per volt the input signal's
amplitude will produce. This is a voltage to frequency slope control.
To use the module with manual settings only, don't insert a lead in the "PROGram FREQuency" input.

SETTING TONE AMPLITUDE

The amplitude is set by the amplitude adjust knob. The switch point at the most clockwise point of rotation of the
amplitude control knob is a calibrated, 1V RMS signal level. Clicking off of this position allows setting the signal
level from slightly above 1V down to zero as the knob is turned counterclockwise.
Like the frequency controls, the function of the manual amplitude control is redefined by the insertion of a lead in
the "PROGram AMPLitude" input on the back panel. With a lead in place, the knob controls the slope of the tone
amplitude as a function of the control signal amplitude in a manner analogous to the frequency controls. Use a
signal here to control amplitude modulation. There is no shaping of controlled amplitude transitions so amplitude
modulation will follow the modulator signal. Shaped transitions in the amplitude domain are used in the "Gate"
and "Attenuation" functions (see below).
To use the module with manual settings only, don't insert a lead in the "PROGram AMPLitude" input.

SETTING NOISE AMPLITUDE

Noise amplitude is manually set in a manner analogous to setting tone amplitude but it is not programmable at the
source.

GATING SIGNALS ON AND OFF

Signals are gated on and off (presented) by the shaped-rise gate control. The gate control for each channel may
be operated manually from the front panel or by a digital logic input from a computer port or another module. The
logic inputs are next to each attenuator's diagram on the rear panel. Gating the signal on and off is accomplished

by using a nonlinear acoustic shaped rise-fall envelope for click-free switching. There are 5 independent, switchselectable
shaping time constants available for each of the 2 channels.
These time constants also determine the level-to-level shaping when using the programmable attenuators.
To have a signal be on constantly for the entire session, use the "manual" position of the switch above the "gated
on" light in each section.

USING THE ATTENUATORS

The attenuator sections associated with each signal are not manually settable; manual control of signal levels is
accomplished by using the amplitude control. The attenuators are set at zero dB attenuation when no lead is
connected to the attenuator input on the rear panel. The level of attenuation may be controlled by the amplitude
of the signal on this input; 5.080 V equaling full amplitude and 0 V equaling full attenuation.
The 3-position switch associated with each attenuator on the front panel allows the attenuator to: 1) be gated on
manually, or 2), latch the value of the attenuation control signal at the onset of a gate signal, or 3), follow the
changing attenuation control signal for the duration that the gate is asserted. Manual presentations are latched.
The "Latch" mode assures that the amplitude will not vary slightly with small changes in the control signal's
amplitude during a presentation. The "Follow" mode allows the attenuator to follow programmed changes in
80
attenuation during a single presentation (gate "on" interval). In the "Follow" mode, the program can step through a
"staircase" of dB levels, or access random levels without interruption. When following, the shaped-rise-gating
time constant is used to shape the change in attenuation level, thus there is a limitation on "modulation" following
rate analogous to that for frequency modulation noted earlier. Here the limits depend upon the selected time
constant. The shaped transition from level to level of attenuation has a time constant of 1/128th of the value
selected for the gate for each dB of attenuation change.

CONTROL OF EXTERNAL SIGNALS

An external signal (a tone or tone-noise mix from another V85-05C, a signal from a tape recorder or other source)
may be gated and/or attenuated, and/or mixed with a tone from this module. Just introduce the signal at the
"EXTernal Signal" input. If another V85-05c module is used, the tone-noise mix may be controlled at its source
module as well as this module, ultimately allowing two tone signals and a noise signal to be mixed, attenuated,
and gated (with both tones' amplitudes and frequencies modulated), in any combination. This signal can then be
mixed with still another signal from the input marked "EXTernal SIGnal". Add a third module and the possibilities
are too numerous to list here!

AMPLITUDE RANGE

The range of absolute Sound Pressure Level amplitudes available for stimulus presentation is not limited to the

dB attenuation range of the attenuator section. The signal source voltage level can be set independently, ahead
of the attenuator section. Thus, the reference amplitude is set by manual control (or in the case of tones, also by
program control) at the source before the attenuation is applied permitting very small changes and very low
absolute levels of output with minimum noise. Set the signal source amplitude control and your power amplifier to
produce the desired starting amplitude in dB-SPL in the environment, and then attenuate from that point.
The amplitude control knob (or in the case of tones, the programmed amplitude input as well) may be used to set
the desired maximum signal level going to an external amplifier and the output transducer. This sets the source
amplitude prior to routing through the programmable attenuators to control programmed sequences of
presentations of different (attenuated) amplitudes. Since amplitude levels may also be programmed at the
source, you may change absolute values of the reference dB-SPL and attenuate over any range all under
program control.

MODULATION

Modulation of either tone frequency (with limitations - see specifications) or amplitude may be accomplished at
the tone source. Tone, noise and external signals may be modulated across the dB scale by the attenuators. The
modulator signal, if it is bipolar, must be offset because the negative regions of control inputs for frequency,
amplitude and attenuation cannot effect changes in the signal.

MONOPHONIC, BINAURAL AND STEREOPHONIC OPERATION

Use the mixed output to a single ear for monophonic presentations. Connect the mixed output to both channels
of a stereo amplifier with a "Y" connector for binaural use. Connect the two unmixed outputs to separate
channels of a stereo amplifier for stereo operation.

FRONT PANEL CONTROL FUNCTIONS

4-Digit Switch Bank - Sets frequency directly in the manual mode (no lead in the program input) and controls the
frequency as a function of the voltage present on the program input when a lead is in place. In the program mode
(lead in place) the switches set Hz per Volt of the control signal. Note: The absolute minimum setting is 10 Hz;
below this the oscillator may stop oscillating and will have to be set to a higher value to resume.

Frequency Range Switch - Multiplier for the 4-digit frequency switch, 0.01 times, 0.1 times, 1 times and 10 times
the digital setting.

Amplitude Adjust Knob, Tone - Adjusts the amplitude of the tone source from 0 to 1.2 Volts when no lead is in
the program input on the rear panel. The switch position at the end of travel sets a calibrated 1V RMS signal.

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With this switch setting and a lead in the control input, the knob control gives 250 mV RMS of tone amplitude per
Volt of control signal amplitude.

Amplitude Adjust Knob, Noise - Adjusts the amplitude of the tone source from 0 to 1.2 Volts. The switch
position at the end of travel sets a calibrated 1V RMS signal.
Gate/Attenuator Control Switches (2) - These 3-position switches, one each in the tone section and the noise
section, control how the attenuator behaves during a presentation (gate "on") and also allow manual presentation
of a signal.
The up, "Follow", position allows the attenuator to follow changes in the attenuator program control input during a
presentation. In the "Follow" position, the transitions are shaped by 1/128th of the selected time constant of the
rise/fall shaping control for each dB step of change. This allows signals to be modulated in dB as a function of a
linear control voltage provided the modulator is of lower frequency than the rate of change of the shaping time
constant.
The center position, "L", causes the attenuator to latch the value on the program control input at the onset of a
gate command and to hold that level through the entire presentation regardless of changes in the program control
voltage during presentation. This permits setup of the next level during presentation.
The down, "Manual", position, turns the channel gate "on". Manual presentations are latched.
"Gated On" LED Lights (2) - These lights are on for the duration that a signal is being presented.
Shaped-Rise Gate Control Switches (2) - These allow the user to select the time constant for the shaping
envelope. Select instantaneous (<1 millisecond), 5 millisecond, 10 millisecond, 50 millisecond or 100 millisecond
time constants. This control also selects the attenuation-transition shaping at the rate of 1/128th of the selected
value per dB-step of change.
FALL TIME
FULL
AMPLITUDE
TIME
RISE TIME
STIMULUS
ON TIME
DIGITAL CONTROL SIGNAL
FULL AMPLITUDE
Progressively shorter control signal on-times
with the same rise-time, reduces the fullamplitude
time to the point that the signal
can never reach full amplitude.
With shorter control signal on-times
and shorter rise-times, the signal can
still reach full amplitude.
82
REAR PANEL CONNECTION FUNCTIONS (LEFT TO RIGHT)
PROGram FREQuency - An analog voltage on this input sets the frequency of the tone. Inserting a lead in this
input automatically changes the direct frequency-control function of the 4-digit switch and range toggle switch.
Frequency is now controlled by the voltage present on this input (from 0 to 9.6V) times the switch settings. For

example, 4000 on the 4-digit switch and "B" on the range switch with a 2.5 volt input on this lead will produce a 1K
Hz tone (400 x 2.5 = 1000 Hz).
Bandwidth Limit, "A" position - 10* Hz to 99 Hz.
Bandwidth Limit, "B" position - 50 Hz to 999 Hz.
Bandwidth Limit, "C" position - 500 Hz to 9999 Hz.
Bandwidth Limit, "D" position - 5K Hz to 99.99 KHz.
*Note the minimum settable or programmable frequency is 10 Hz (see specifications).
PROGram AMPLitude - When a lead is in this input it automatically changes the function of the amplitude
control knob to multiply the voltage on the input by approximately .250 times the control setting. Thus it takes
approximately a 4-Volt control signal to produce a 1 Volt RMS tone when the control is in the switch-locked (1 Volt
calibrated) position. This range may be adjusted cursively from 0 to 120% of the value by setting the knob in an
"off calibrated" position.
Tone Out - This is the oscillator output, manually or program controlled for frequency and amplitude. It is
unmodified by attenuation and is not gated.
Noise Out - This is the raw noise source output as set by the manual amplitude control. It is unmodified by
attenuation and is not gated.
EXTernal Signal - This is an input for an external signal from any other source including another V85-05C
module. It is provided so that other signals may be attenuated and gated and/or mixed with the tone channel.
Using this input disconnects the noise source and replaces it, allowing this signal to be passed through
attenuator, gate, and mixer to the outputs. Since two noise sources are generally not used in audio signal
complexes, the noise source is the one to sacrifice. If a complex signal consisting of more than one tone along
with noise is desired, the noise and first tone along with initial amplitude control, attenuation, gating and mixing is
synthesized at another V85-05C module. Then it is introduced to this module at the EXTernal Signal input to be
further attenuated, gated, etc. and finally mixed with the second tone, synthesized here.
Programmable Attenuator In (2) - The two attenuators, one each in the tone and noise channels, function
identically. The analog signal on this input controls the level of attenuation of the signal from the sources.
Attenuation is controlled in 1-dB steps from 0 to -127 dB. 1 dB of attenuation is produced for each 40 mV of
control signal amplitude. To minimize the possibility of a noisy control signal producing one more or one less
level of attenuation than intended, the transitions start at 20 mV, giving an ample 20 mV margin for noise riding on
the control signal.
0 dB = 5.080 V
-1 dB = 5.040 mV
-2 dB = 5.000 mV
-126 dB = 40 mV
-127 dB = 0 V
An envelope equal to 1/128th of the gate-envelope time per dB step shapes attenuation transitions accomplished

during a presentation (gate on).
Gate Controls (2) - The gate controls associated with each channel require a standard system logic 1 (low true)
to operate. When operated, the channel is gated on and the signal is presented. The gate uses shaped rise
circuitry to produce click-free onsets and offsets of the stimulus. Select instantaneous (<1 millisecond), 5
millisecond, 10 millisecond, 25 millisecond or 50 millisecond time constants.
EXTernal SIGnal Input - This input is available for introducing yet another signal (in addition to the one ahead of
the attenuator and gate) into the stimulus complex. This one is introduced past the attenuators and gate controls
83
and taken only to the mixer. As with the other input, EXTernal Signal to the left, it may be from any source
including another V85-05C where all functions may be performed before introduction to this input.
Noise/EXTernal Out - This is the attenuated and gated noise source signal or the attenuated and gated EXTernal
Signal output prior to mixing with other signals.
Mix Out - This is a linear (even) mix of the 3 signals, (tone), (noise / EXTernal Signal), and (EXTernal SIGnal).
There is no gain in any channel or in the mixer. Signals are summed at the levels present on the inputs to the
mixer stage.
Tone Out - This is the manual or programmed frequency and/or amplitude, attenuated and gated tone signal
output prior to mixing with other signals.

SPECIFICATIONS V85-05C (Rev. C on PC board)

TONE SOURCE

Frequency - 4 Ranges -
Manual control
"A" position - 10* Hz to 99 Hz.
"B" position - 50 Hz to 999 Hz.
"C" position - 500 Hz to 9999 Hz.
"D" position - 5K Hz to 99.99 KHz
"P" position - Permits program control via jacks on the rear panel adjacent to the "Tone Source" box.
Program control (Right jack is LSB)
00 = "A" = 10* Hz to 99 Hz.
01 = "B" = 50 Hz to 999 Hz.
10 = "C" = 500 Hz to 9999 Hz.
11 = "D" = 5K Hz to 99.99 KHz
Amplitude: 0 to 1.5 V RMS - 1.00 V RMS calibrated.
Frequency Control Voltage: 40 mV* to 9.6 V (depends on settings of frequency control switches).
Amplitude Control Voltage: 0 to 4 V
Control Input Impedance: > 1 MW
Frequency Accuracy: The greater of 2% or 2Hz.
Frequency Linearity: 10:1 Sweep - 2%
Frequency Linearity: Full Range Sweep - 8%
Amplitude Modulation Linearity: 2%
Amplitude Stability: 0.5 dB
Sine Wave Distortion: 0.5%

NOISE SOURCE

Amplitude: 0 to 1.5 Volt peak max.

Frequency Band: 10 Hz to 20 KHz (White)
Flatness: ± 2 dB
84

ATTENUATORS

Attenuation Control Range: 0 to -127 dB (Dynamic Range 100dB - noise floor to clip.)
Attenuation Step Size: 1 dB
Attenuation Shaping (in follow mode): 1/128th of selected rise/fall shaping time constant per dB step.
Channel Separation: 80 dB
Noise Floor: 90 dB.
Total Harmonic Distortion + Noise: 0.01%
Control Voltage: 0 to 5.080 V
Control Voltage Step Size: 40 mV
Control Input Impedance: > 1 MW
Mute Voltage: 0 V

GATE CONTROL (Standard Logic Levels)

Gate Attenuation: -95 dB
Shaping Time Constants: <0.1, 5, 10, 25, 50 ms (Time from 10% to 90% of full amplitude).

EXTERNAL AUDIO SIGNAL INPUTS

Input Voltage: 0 to 1.2 V RMS
Input Impedance: > 1 MW

SIGNAL OUTPUTS

Output Voltage: 0 to 1.2 V RMS
Output Impedance: (>10 Hz) - 2 kW

*** PERFORMANCE LIMITATION NOTES** V85-05C (Rev. A)

***NOTE: THIS UNIT REQUIRES A POWER AMPLIFIER TO DRIVE SPEAKERS*.**

1 - Due to frequency-transition and attenuation-transition shaping circuits, frequency and attenuation modulation
is limited in frequency by the time constants of these circuits (15 Hz). Amplitude modulation is not limited to this
frequency.
2 - The minimum settable or programmable frequency of the oscillator is 10 Hz. If you set it or program it below
this value it may cease to oscillate and not resume until the (manually set or controlled) frequency returns to a
value above 10 Hz.
3 - Although there are 4 digits in the frequency control switch bank, this does not imply the precision of the set
points. See pages E and F.

Appendix p
Day Two Exclusionary Review

Subject ID_____ **Date**_____

Day Two Exclusionary Review Sheet

Exclusion criteria - Explicitly ask subjects if any of the following apply to them.

1. Do you have any implanted cardiac devices (demand-type cardiac pacemaker or implanted defibrillator)?_____
2. Are you currently in pain?_____
3. Are you taking any medications that would alter your ability to feel pain?_____
4. Have you had any recent surgical procedures?_____
5. Are you currently pregnant? – all female subjects must have a negative pregnancy test-result within a week of today if they are to participate_____
6. Do you have Asthma?_____
7. Do you have a history of psychiatric illness, for example, panic disorder?_____
8. Do you have or have you ever been diagnosed with:
    - cardiac arrhythmias_____
    - heart disease_____
    - vascular/circulation problems_____
    - blood clotting disorders_____
    - epilepsy or any history of seizures_____
    - sensory nerve damage_____
    - abnormal skin or skin damage_____

When was the last time you consumed?

1-Caffeine_____

2-Alcohol_____

3-Any Pain Medication_____

Name of Medication_____

Researcher's Name_____

June 6, 2007

Institutional Review Board
2100 Lee Building
University of Maryland
College Park, MD 20742

Re: 07-0187 (PAS 1720), "Performance Under Pressure: …"

Dear Committee Members,

Besides being a full-time PhD student in the neuroscience and cognitive sciences program for the past four years, I've been licensed by the state of Maryland as a chiropractor with physical therapy privileges (license#: 01837-PT) since July of 1997. The state chiropractic board of examiners only issues this type of license to Doctors of Chiropractic who have successfully completed specific coursework and have passed the physiotherapy section of the national board exam.

I have used TENS devices in my practice for the past ten years. TENS was developed in the early 70's after Melzack and Wall (1965) advanced the gate theory of pain control. These devices are widely used in the United States, Canada and many European countries. In July of 2006 the BBC reported an estimated 450,000 uses annually in Canadian hospitals alone. TENS units in the United States are regulated by the FDA and most often are prescribed by physicians for patients to use at home and as such are designed for ease of use.

I plan to personally oversee the training of all researchers' involved in this project. This training will consist of correct electrode placement, devices operation and guidelines for safe use of TENS. We have made changes to appendix i the 'TENS Safety List Sign-Off for Researchers' which reflect the fact that I will oversee on two different occasions and sign-off that all researchers have read and understood the Safety Precautions and demonstrated on another researcher the proper set up and use of the TENS electrodes and unit.

Please feel free to contact me if there are any questions.

Sincerely,

Mark Saffer, DC

Department of Kinesiology
NACS program
Cognitive Motor Neuroscience Lab, HLHP BLDG
University of Maryland

Subject ID #_____
Date_____

Script to Read to Participants for Competitive Aspect of Performance Under Pressure Study

1- Hello, I would like to tell you now about the competition part of the study.
2- First, the competition is optional
3- The competition does not affect or change any aspect or instruction involving this study, it is only an add-on for additional incentive during the task
4- The competition is based on two factors of the working memory task you will be engaged in, i)-the number of correct responses, ii)-and the average speed (Reaction Time) of the correct responses only
5- The Rewards are as follows;
   1st Prize = $150
   2nd Prize = $100
   3rd Prize = $50
6- You do not have to finish the task to be entered in the competition, it is strictly based on the two above cited criteria (accuracy & reaction time)
7- The study is Scheduled to be finished in the first half of December 2007 and rewards are Scheduled to be distributed before Christmas / New years 2008, if this changes you will be contacted by phone and email
8- In the event of a tie, place prizes will be split accordingly (ex.- 2nd place tie between two participants = $50/each).
9- Your odds of winning will be between 1 in 10 & 1 in 12

10- Do you wish to compete_____

Script -- Working Memory Task Instructions

The task you are about to perform is a memory task. First and foremost you must answer the questions as quickly and accurately as possible. There are two different types of memory task:

Do not worry as we will give you a few sample trials, so you will understand the task and you will be able to ask questions to clarify anything that is not clear.

1-A verbal working memory task in which you will see images of letters projected on the screen, your job is to remember a certain letter---a series of yellow colored letters will be presented on the screen one at a time after the last yellow letter is presented a purple colored letter will appear. You must decide if the purple letter is the same letter as the letter presented 2-letters-back

2-A spatial working memory task in which you will see images of rectangles projected on the screen, your job is to remember where a certain rectangle was ---in the center of each image you will see a yellow letter 'x' additionally around the letter 'x' a single white rectangle will be presented at various positions when the central letter 'x' is purple you must decide if the position of the rectangle presented with the purple letter 'x' is the same position as the position presented 2-positions-back.

Now if you look at the table to your right you will see a response pad with a rectangular-green button and next to it a circular-white button

You should place your right index finger on the green button and your middle finger on the white button

---When you press the green button you are answering **'YES'**, to the question was the purple letter or the white rectangle presented with the purple 'x' the same as the letter or position 2-images-back

---When you press the white button you are answering '**NO'**

Remember--First and foremost you must answer the questions as quickly and accurately as possible.

UNIVERSITY OF MARYLAND
DEPARTMENT OF KINESIOLOGY

2351 HHP Building
College Park, Maryland 20742-2611
TEL 301.405.2450 FAX 301.405.5578
www.hhp.umd.edu/knes

PERFORMANCE UNDER PRESSURE STUDY
PAYMENT VOUCHER

Instructions: Take this completed voucher to Ms. Regina Clary, KNES Business Office, 2334 HHP, x5-2506

_____ _____ _____
(Print Name) (Date) (Amount)

_____
Permanent Address: Street, City, State, Zip

_____
Signature Social Security Number

Signature of Authorized Research Staff _____DATE:_____

PLEASE
DO NOT **EAT**, **DRINK**, **CHEW GUM**, or **RINSE** YOUR MOUTH FOR AT LEAST **ONE HOUR** BEFORE COLLECTING THE SALIVA SAMPLE!

****Best if done right after waking up before brushing teeth, eating breakfast, or drinking anything****

Directions for Collecting DNA Sample:

1) Open bottle of Scope. Open the collection tube and fill with mouthwash to the black fill line (10mL).

2) SWISH the mouthwash from the tube around in your mouth vigorously for **ONE MINUTE. Watch a clock when doing this!**

   DO NOT GARGLE or CLEAR THROAT! SWISH ONLY.

3) Holding the tube close to your mouth, spit the mouthwash back into the tube. Replace the top on the tube and screw it on tightly.

4) Mail the sample within 24 hours of collection (see below)! Keep sample at room temperature.

Mailing Directions:

1) Place the collection container into the Ziploc bag with the absorbent sheet. Do not remove the absorbent sheet in case of spillage.

2) Remove any air from Ziploc bag and seal.

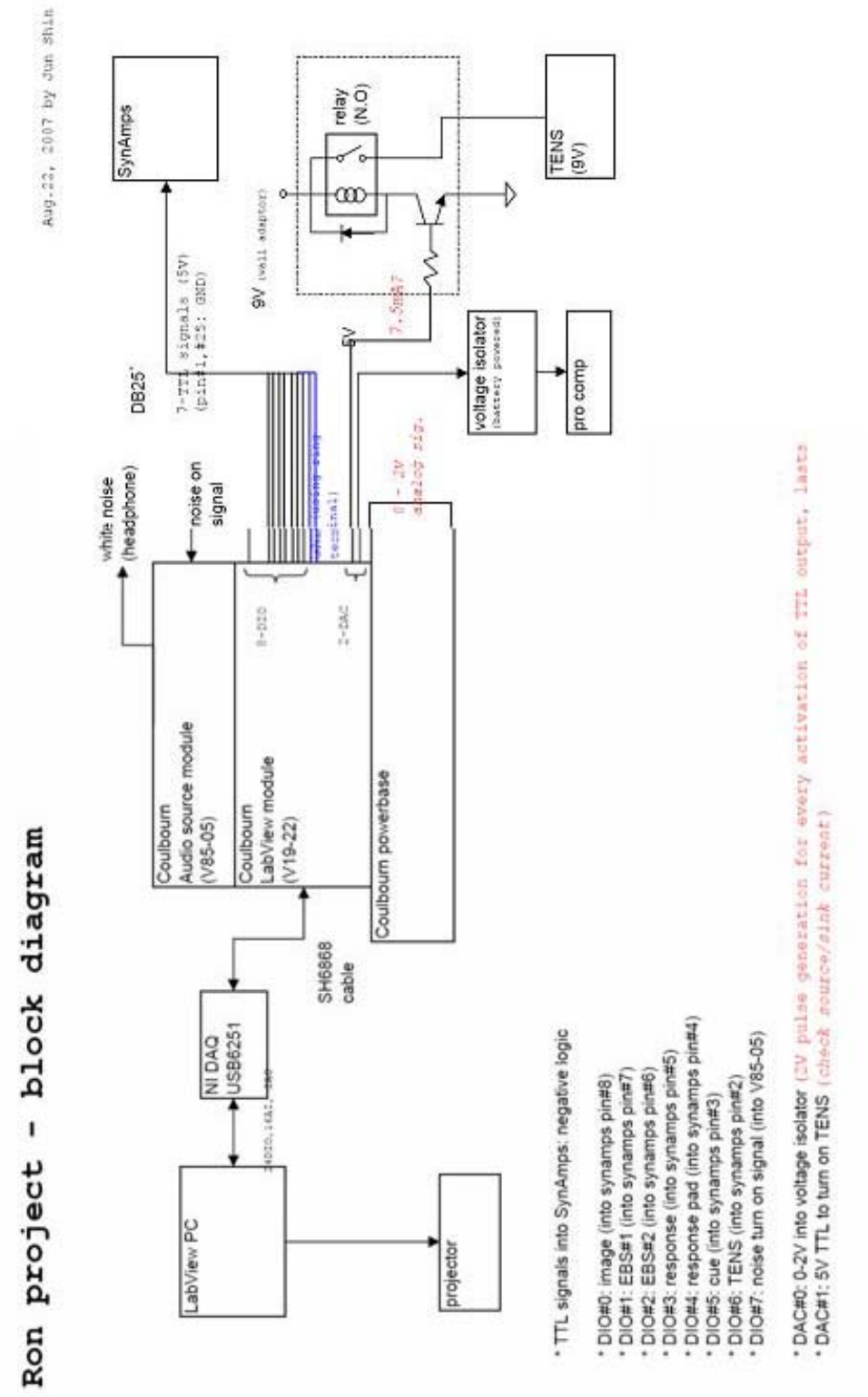
3) Place Ziploc bag in second Ziploc bag. Place contents into mailing envelope addressed to the University of Maryland.

4) If appropriate, place one copy of the signed consent form (the second copy is for your records), the completed questionnaire, the completed medical records release form, and the completed Relative Information Sheet into the envelope with your mouthwash sample and seal the envelope.

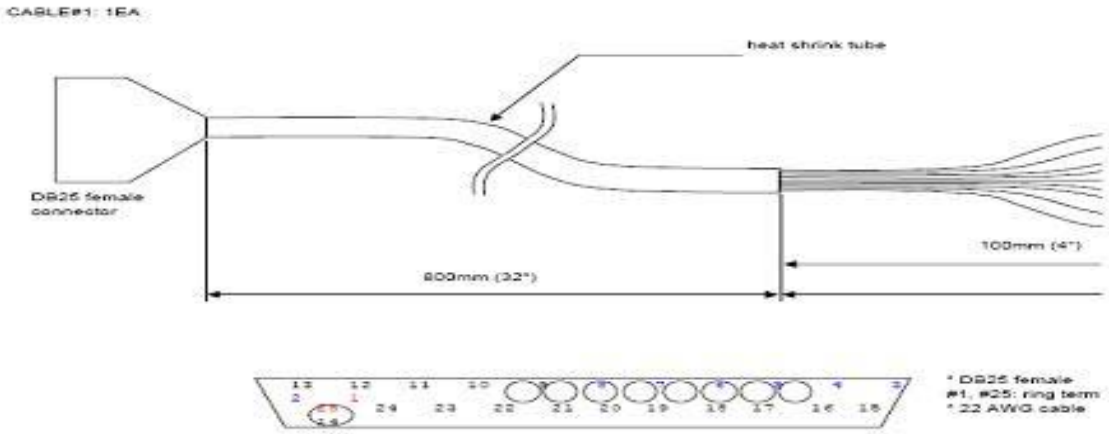
Thank you for your participation!

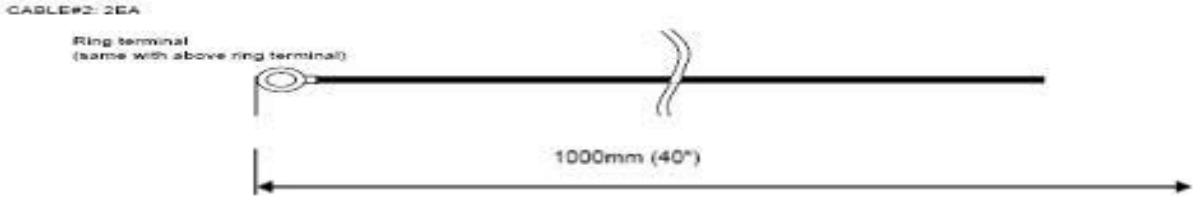
If you have any questions, please feel free to contact the study coordinator, Ron Goodman, at 301-405-6872

Appendix II: Wiring Diagram




bit7 bit6 bit5 bit4 ... bit0
1 2 3 4 5 6 7 8 9 10 11 12 13
14 15 16 17 18 19 20 21 22 23 24 25
* DB25 female (cable side)
#1,#26: GND, #2-#8: 5V TTL signal


CABLE#1: 1EA
heat shrink tube
DB25 female connector
100mm (4")
800mm (32")
* DB25 female
#1, #25: ring term
* 22 AWG cable


CABLE#2: 2EA
Ring terminal
(same with above ring terminal)
1000mm (40")

Cable 1 & 2

Appendix III: Matlab Code for Signal Processing

```
Appendix 3

function [epochDataList_2D,numSamples,epochNum,Sf] =
eeg32_cnt_2_Ch(eventfile);
fid=fopen(eventfile);
header=textscan(fid,'%s %s%*[^\n]',20);

epochTemp = header{2}(10);%Number of epochs
epochNum = str2num(epochTemp{1}); % e.g. 139

numChanTemp = header{2}(4);%Number of channels
numChan = str2num(numChanTemp{1});

SampFreqTemp = header{2}(5);%Number of samples per epoch
Sf = round(str2num(SampFreqTemp{1}));

numSamplesTemp = header{2}(8);%Number of samples per epoch
numSamples = str2num(numSamplesTemp{1});

acceptList=zeros(epochNum,1);
%epochDataList=zeros(256,9,epochNum); % each element 1 or 0
epochDataList=zeros(numSamples,2,epochNum); % each element 1 or 0

for epoch=1:epochNum

    epochHeader=textscan(fid,'%s %s%*[^\n]',7);
    acceptTemp=epochHeader{2}(3);
    accept=str2num(acceptTemp{1}); % 1 or 0 (accept or reject)

    %epochData=textscan(fid,'%f %f %f %f %f %f %f %f %f%f',256);
    %epochData=textscan(fid,'1%f %f 3%f 4%f 5%f 6%f 7%f 8%f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f',numSamples);

epochData=textscan(fid,'%f %f',numSamples);   %f %f %f %f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f
epochDataMatrix=[epochData{:}]; % 2048 samples by 50 electrodes

    acceptList(epoch)=accept; % append to list
    epochDataList(:,:,epoch)=epochDataMatrix; % append to list

end

fclose(fid);

seltnumChan=size(epochData,2);
```

```
%now analyze

sumAccepted=zeros(numSamples,seltnumChan);
%finding the mean of each electrode
for epoch=1:epochNum
    if acceptList(epoch) == 1
        sumAccepted=sumAccepted+epochDataList(:,:,epoch);
    end
end

% meanOverEpochs=sumAccepted/sum(acceptList);
% figure(1);plot(meanOverEpochs)

%change from 3D to 2D
for epoch=1:epochNum
    lo = 1+(epoch-1)*numSamples;
    hi = epoch*numSamples;
    epochDataList_2D(lo:hi,:)=epochDataList(:,:,epoch);
end


function [epochDataList_2D,numSamples,epochNum,Sf] =
eeg32_cnt_4_Ch(eventfile);
fid=fopen(eventfile);
header=textscan(fid,'%s %s%*[^\n]',20);

epochTemp = header{2}(10);%Number of epochs
epochNum = str2num(epochTemp{1}); % e.g. 139

numChanTemp = header{2}(4);%Number of channels
numChan = str2num(numChanTemp{1});

SampFreqTemp = header{2}(5);%Number of samples per epoch
Sf = round(str2num(SampFreqTemp{1}));

numSamplesTemp = header{2}(8);%Number of samples per epoch
numSamples = str2num(numSamplesTemp{1});

acceptList=zeros(epochNum,1);
%epochDataList=zeros(256,9,epochNum); % each element 1 or 0
epochDataList=zeros(numSamples,4,epochNum); % each element 1 or 0

for epoch=1:epochNum

    epochHeader=textscan(fid,'%s %s%*[^\n]',7);
    acceptTemp=epochHeader{2}(3);
    accept=str2num(acceptTemp{1}); % 1 or 0 (accept or reject)

    %epochData=textscan(fid,'%f %f %f %f %f %f %f %f %f%f',256);
    %epochData=textscan(fid,'1%f %f 3%f 4%f 5%f 6%f 7%f 8%f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f',numSamples);
```

```
epochData=textscan(fid,'%f %f %f %f',numSamples);   %f %f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f
%f %f
epochDataMatrix=[epochData{:}]; % 2048 samples by 50 electrodes

    acceptList(epoch)=accept; % append to list
    epochDataList(:,:,epoch)=epochDataMatrix; % append to list

end

fclose(fid);

seltnumChan=size(epochData,2);

%now analyze

sumAccepted=zeros(numSamples,seltnumChan);
%finding the mean of each electrode
for epoch=1:epochNum
    if acceptList(epoch) == 1
        sumAccepted=sumAccepted+epochDataList(:,:,epoch);
    end
end

% meanOverEpochs=sumAccepted/sum(acceptList);
% figure(1);plot(meanOverEpochs)

%change from 3D to 2D
for epoch=1:epochNum
    lo = 1+(epoch-1)*numSamples;
    hi = epoch*numSamples;
    epochDataList_2D(lo:hi,:)=epochDataList(:,:,epoch);
end

function [B_L_Fads] = PUP_D1_Fads(numSamples,numEpoc,Sf,F3,F4);

for i=1:numEpoc,
    low=1+numSamples*(i-1);
    high=numSamples*i;
    F3_epoc(:,i)=F3(low:high,:);
    F4_epoc(:,i)=F4(low:high,:);
end

  for i=1:numEpoc

[psd_F3_epoc(:,i),F]=pwelch(F3_epoc(:,i),hamming(Sf),[],[],Sf);
      log_alpha_pwr_F3_epoc(i)=log(sum(psd_F3_epoc(9:14,i)));

[psd_F4_epoc(:,i),F]=pwelch(F4_epoc(:,i),hamming(Sf),[],[],Sf);
      log_alpha_pwr_F4_epoc(i)=log(sum(psd_F4_epoc(9:14,i)));
  end

  Fads=log_alpha_pwr_F4_epoc-log_alpha_pwr_F3_epoc;
  B_L_Fads=mean(Fads);
```

```
  varFads=std(Fads);



function [B_L_Fads,varFads,HiMean,LowMean] =
PUP_D2_Fads_b(numSamples,numEpoc,Sf,F3,F4);

for i=1:numEpoc,
    low=1+numSamples*(i-1);
    high=numSamples*i;
    F3_epoc(:,i)=F3(low:high,:);
    F4_epoc(:,i)=F4(low:high,:);
end

  for i=1:numEpoc

[psd_F3_epoc(:,i),F]=pwelch(F3_epoc(:,i),hamming(Sf),[],[],Sf);
      log_alpha_pwr_F3_epoc(i)=log(sum(psd_F3_epoc(9:14,i)));

[psd_F4_epoc(:,i),F]=pwelch(F4_epoc(:,i),hamming(Sf),[],[],Sf);
      log_alpha_pwr_F4_epoc(i)=log(sum(psd_F4_epoc(9:14,i)));
  end

  Fads=log_alpha_pwr_F4_epoc-log_alpha_pwr_F3_epoc;
  B_L_Fads=mean(Fads);
  varFads=std(Fads);

   [sort_epocs,ind_epocs]=sort(Fads,(2),'descend');  % Sorts Frontal
Asymmetry scores with their values and indices

  epocs_mat=[sort_epocs' ind_epocs'];                % Makes a 2
column matrix with epoch asym scores on left & index on right

    Hiten= [epocs_mat(1:10,:)];
    Lowten=[epocs_mat(numEpoc-9:numEpoc,:)];

   HiMean=mean(Hiten(:,1));
   LowMean=mean(Lowten(:,1));







pth = uigetdir('C:\','Select location of subjects files');
%allows you pick folder
eval(['cd ',pth]);                                    %changes
directory to file loc

x = input('Please enter total number of subjects ');
```

```
names = ['C1S';'C1V';'C2S';'C2V';'C3S';'C3V';'ECL';'EOP'];
values = ['HR_avg';'HR_std';'SC_max';'SC_min';'SC_avg';'SC_std'];
c = 1;
datamatrix = cell(x+1,49);
for s = 1:8
    for t = 1:6
        c = c + 1;
        datamatrix{1,c} = strcat(names(s,:),'_',values(t,:));
    end
end
datamatrix{1,1} = 'sub_ID';

for i = 1:x;
%This part gets the list of the files in the folder to pick from
d = dir;
str = {d.name};
n = strcat('Choose all files for the_',num2str(i),'th subject');
[s] = listdlg('Name',n,...
    'OKString','Run it','CancelString','I Screwed Up','ListSize',...
    [300,400],'PromptString','Select a file:','SelectionMode',...
    'multiple','ListString',str);

%In case someone hits 'select all' or chooses the index files (. ..)
%This loop will get rid of those files to avoid future errors
    if   s(1) == 1 || s(1) == 2;
        s = s(2:length(s));
    if s(1) == 2;
        s = s(2:length(s));
    end;
    end;

files = str(s); %Creates a variable of just the files that were
choosen
datamatrix{i+1,1} = files{1,1}(8:9);
    for j = 1:8
    a=[pth '\' files{j}];
        fid=fopen(a);
        header=textscan(fid,'%s %s%*[^\n]',4);
        data = textscan(fid,'%f %f %f %f %f %f %f %f %f %f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f
%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f
%f %f %f %f %f','delimiter',',');
        datamatrix(i+1,((6*j)-4):((6*j)+1)) = data([17 18 45 46 47
48]);
    end

end;

close all
clear all
clc
%----------
%Definition
%Fs = 1024;
%----------
```

```
path_data = cd ('C:\PUP_D2_EO_EC_ONLY\PUP_D2_EOEC_ASCI_lf');
%
%eval(['cd ', path_data])
eval(['dir']);
d=dir;
Nfolders=length(dir);
counter = 0;
for i_folder=3:Nfolders,
    counter = counter + 1
    eventfile=d(i_folder).name;

    %-----------------------------------------------------------------
-----------
    %Read CNT files
    %eventfile =
'LS_SUM_05_005_ST_bl_OAR_bp_EP_blc_SF_dre_ASCI.dat'; %&&&
    [cont_eeg_file,numSamples,numEpoc,Sf] =
eeg32_cnt_2_Ch(eventfile);


     F3=cont_eeg_file(:,1);
     F4=cont_eeg_file(:,2);


     [B_L_Fads] = PUP_D1_Fads(numSamples,numEpoc,Sf,F3,F4);

     Fads_mtrx_D1(counter,:)=B_L_Fads;

     namesfiles(i_folder,:)=eventfile;
     %namesfilesAdj = namesfiles(3:length(namesfiles),:)

Fads_mtrx_indx_D1(counter,1) = {namesfiles(counter+2,1:9)};  % Note
squiggly brackets of Cell Matrix
Fads_mtrx_indx_D1(counter,2) = {Fads_mtrx_D1(counter,:)};

end

  [MaxFads,Indmax]=max(Fads_mtrx_D1);
  [MinFads,Indmin]=min(Fads_mtrx_D1);

  no_pos_scores=length(find(Fads_mtrx_D1>0));  % This gives the # of
positive scores
  no_neg_scores=length(find(Fads_mtrx_D1<0));
  id=10:61
  [sort_epocs,id]=sort( Fads_mtrx_D1,(1),'descend');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%


id=10:61

close all
clear all
clc
```

```
%----------
%Definition
%Fs = 1024;
%----------

path_data = cd ('C:\PUP_D2_EO_EC_ONLY\PUP_D2_EOEC_ASCI_lf');
%
%eval(['cd ', path_data])
eval(['dir']);
d=dir;
Nfolders=length(dir);
counter = 0;
for i_folder=3:Nfolders,
    counter = counter + 1
    eventfile=d(i_folder).name;

    %-----------------------------------------------------------------
-----------
    %Read CNT files
    %eventfile =
'LS_SUM_05_005_ST_bl_OAR_bp_EP_blc_SF_dre_ASCI.dat'; %&&&
    [cont_eeg_file,numSamples,numEpoc,Sf] =
eeg32_cnt_2_Ch(eventfile);


     F3=cont_eeg_file(:,1);
     F4=cont_eeg_file(:,2);


     [B_L_Fads] = PUP_D1_Fads(numSamples,numEpoc,Sf,F3,F4);

     Fads_mtrx_D1(counter,:)=B_L_Fads;

     namesfiles(i_folder,:)=eventfile;
     %namesfilesAdj = namesfiles(3:length(namesfiles),:)

Fads_mtrx_indx_D1(counter,1) = {namesfiles(counter+2,1:9)};  % Note
squiggly brackets of Cell Matrix
Fads_mtrx_indx_D1(counter,2) = {Fads_mtrx_D1(counter,:)};

end

  [MaxFads,Indmax]=max(Fads_mtrx_D1);
  [MinFads,Indmin]=min(Fads_mtrx_D1);

  no_pos_scores=length(find(Fads_mtrx_D1>0));  % This gives the # of
positive scores
  no_neg_scores=length(find(Fads_mtrx_D1<0));
  id=10:61
  [sort_epocs,id]=sort( Fads_mtrx_D1,(1),'descend');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%
```

```
id=10:61

close all
clear all
clc
%----------
%Definition
%Fs = 1024;
%----------

path_data = cd
('C:\PUP_2008\PUP_D2_Cond_Fads_ASCI\PUP_D2_C3V_Fads_ASCI');
%
%eval(['cd ', path_data])
eval(['dir']);
d=dir;
Nfolders=length(dir);
counter = 0;
for i_folder=3:Nfolders,
    counter = counter + 1
    eventfile=d(i_folder).name;

    %-----------------------------------------------------------------
-----------
    %Read CNT files
    %eventfile =
'LS_SUM_05_005_ST_bl_OAR_bp_EP_blc_SF_dre_ASCI.dat'; %&&&
    [cont_eeg_file,numSamples,numEpoc,Sf] =
eeg32_cnt_2_Ch(eventfile);


     F3=cont_eeg_file(:,1);
     F4=cont_eeg_file(:,2);


     [B_L_Fads,varFads,HiMean,LowMean] =
PUP_D2_Fads_b(numSamples,numEpoc,Sf,F3,F4);

     Fads_mtrx_D2(counter,:)=B_L_Fads;
      Fads_mtrx_D2var(counter,:)=varFads;
       Fads_mtrx_D2HM(counter,:)=HiMean;
        Fads_mtrx_D2LM(counter,:)=LowMean;

     namesfiles(i_folder,:)=eventfile;
     %namesfilesAdj = namesfiles(3:length(namesfiles),:)

Fads_mtrx_indx_D2(counter,1) = {namesfiles(counter+2,1:13)};  % Note
squiggly brackets of Cell Matrix
Fads_mtrx_indx_D2(counter,2) = {Fads_mtrx_D2(counter,:)};
Fads_mtrx_indx_D2(counter,3) = {Fads_mtrx_D2var(counter,:)};
Fads_mtrx_indx_D2(counter,4) = {Fads_mtrx_D2HM(counter,:)};
Fads_mtrx_indx_D2(counter,5) = {Fads_mtrx_D2LM(counter,:)};
end
```

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%
 [sort_epocs,ind_epocs]=sort(Fads,(2),'descend');  % Sorts Frontal
Asymmetry scores with their values and indices

  epocs_mat=[sort_epocs' ind_epocs'];                % Makes a 2
column matrix with epoch asym scores on left & index on right

    Hiten= [epocs_mat(1:10,:)];
    Lowten=[epocs_mat(numEpoc-9:numEpoc,:)];

   HiMean=mean(Hiten(:,1))
   LowMean=mean(Lowten(:,1))

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%
  [MaxFads,Indmax]=max(Fads_mtrx_D2);
  [MinFads,Indmin]=min(Fads_mtrx_D2);

  no_pos_scores=length(find(Fads_mtrx_D2>0));  % This gives the # of
positive scores
  no_neg_scores=length(find(Fads_mtrx_D2<0));
  id=10:61
  [sort_epocs,id]=sort(Fads_mtrx_D2,(1),'descend');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%



id=10:61


pth = 'C:\PUP_2008\PUP_EBS';      %allows you pick folder
eval(['cd ',pth]);                                       %changes
directory to file loc


%This part gets the list of the files in the folder to pick from
d = dir;
str = {d.name};
[s] = listdlg('Name','Choose one subjects files (12 total)...',...
    'OKString','Run it','CancelString','I Screwed Up','ListSize',...
    [300,400],'PromptString','Select a file:','SelectionMode',...
    'multiple','ListString',str);

%In case someone hits 'select all' or chooses the index files (. ..)
%This loop will get rid of those files to avoid future errors
if   s(1) == 1 || s(1) == 2;
        s = s(2:length(s));
  if s(1) == 2;
```

```
        s = s(2:length(s));
  end;
end;

files = str(s); %Creates a variable of just the files that were
choosen
    if length(files) ~= 12
        error('Wrong number of files entered');
    end

time = linspace(-100,400,1251);

for i = 1:2:size(files,2);
                                % Gives flag a value for while loop
    for pair = 0:1
        a=[pth '\' files{i+pair}];
        fid=fopen(a);
        header=textscan(fid,'%s %s%*[^\n]',20);
        epochNum = str2double((header{2}(10)));
        numSamples = str2double((header{2}(8)));

        for epoch=1:epochNum

            epochHeader=textscan(fid,'%s %s%*[^\n]',7);
            epochData=textscan(fid,'%f',numSamples);
            epochDataMatrix=[epochData{:}]; % 2048 samples by 50
electrodes
            epochDataList(:,pair+1,epoch)=epochDataMatrix; % append
to list

        end
    end
        count = 0;
        reviewed_peaks = [];
        corrected_peaks = [];
        for eb = 1:size(epochDataList,3);

            flag = 2;
            [peaks,loc] = max(epochDataList(:,:,eb));
            while flag>1;
                figure(1);
                prog = strcat(num2str(eb),' out of 11,
',num2str(count),' accepted');
                set(gcf,'Name',prog);

                subplot(1,2,1); plot(time,epochDataList(:,1,eb));
hold on;
                a1 = axis; plot([-100,400],[0,0],'k');
plot([0,0],[a1(3),a1(4)],'k'); axis([-100,400,a1(3),a1(4)]);
                plot(time(loc(1)),peaks(1),'ro'); xlabel('time
(msec)'); ylabel('\muV'); title('2');
                subplot(1,2,2); plot(time,epochDataList(:,2,eb));
hold on;
                a1 = axis; plot([-100,400],[0,0],'k');
plot([0,0],[a1(3),a1(4)],'k'); axis([-100,400,a1(3),a1(4)]);
```

```
                plot(time(loc(2)),peaks(2),'ro'); xlabel('time
(msec)'); ylabel('\muV'); title('4');


                % Determines if user is satisfied with the data
series
                button = questdlgfixed('Please select
button','Visual
Inspection','Accept','Accept_w_Revision','Reject','Reject');

                % User is satisfied and the while loop is terminated
                if strcmp(button,'Accept');
                    close(1);
                    flag=1;
                    count = count + 1;
                    reviewed_peaks(count,1:2) = peaks;
                    corrected_peaks(count,1:2) = peaks -
epochDataList(251,:,eb);

                % User is not satisfied an can now pick where to
cleave the data series
                elseif strcmp(button,'Accept_w_Revision');
                    temp = ginput(2);         % Makes a variable
that gives time value of end of accepted data series
                    peaks = temp(:,2)';
                    locc = find(time >= temp(1,1));
                    loccc = find(time >= temp(2,1));
                    loc(1) = locc(1); loc(2) = loccc(1);
                    close(1);                 % Closes the figure
                    flag=2;                   % Repeates the while
loop to see if user is now satisfied with data series
                elseif strcmp(button,'Reject')

                    close(1);
                    flag = 1;

                end
            end


        end
        corrected_peaks(:,3) = corrected_peaks(:,1) -
corrected_peaks(:,2);
        data{1,(i+1)/2} = files{i}(1:31);
        data{2,(i+1)/2} = corrected_peaks;
        data{3,(i+1)/2} = mean(corrected_peaks);
end
na = strcat(files{1}(1:9),'_EBS_scores');
sav = strcat('save(''',na,''',''data'');');
eval(sav);

pth = uigetdir('C:\','Select location of the files');      %allows
you pick folder
eval(['cd ',pth]);                                         %changes
directory to file loc
```

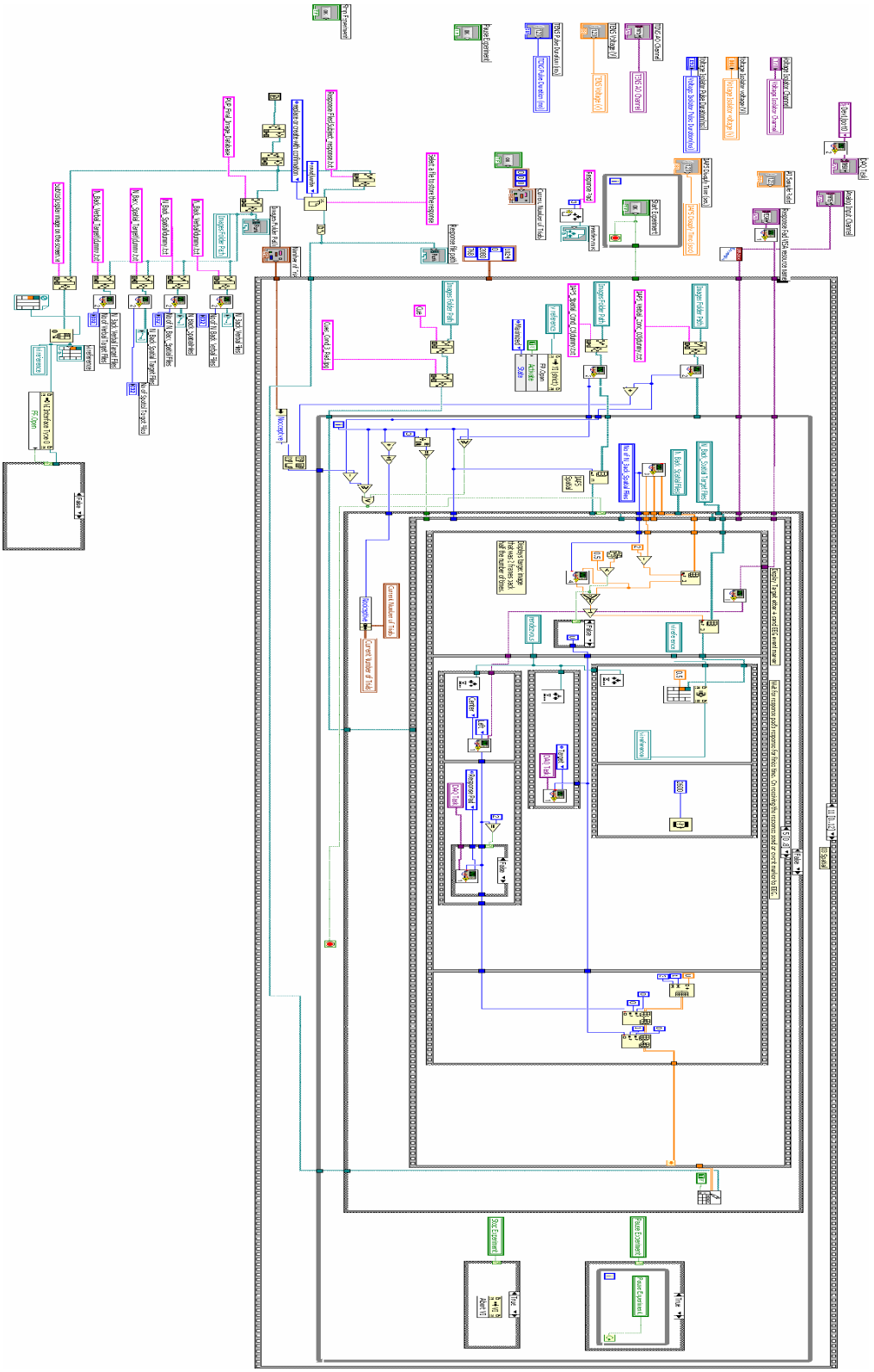
```
%This part gets the list of the files in the folder to pick from
d = dir;
str = {d.name};
[s] = listdlg('Name','Choose your files...',...
    'OKString','Run it','CancelString','I Screwed Up','ListSize',...
    [300,400],'PromptString','Select a file:','SelectionMode',...
    'multiple','ListString',str);

%In case someone hits 'select all' or chooses the index files (. ..)
%This loop will get rid of those files to avoid future errors
if   s(1) == 1 || s(1) == 2;
        s = s(2:length(s));
  if s(1) == 2;
        s = s(2:length(s));
  end;
end;

files = str(s);                 %Creates a variable of just the
files that were choosen
save_count = 1;
names = ['C1S';'C1V';'C2S';'C2V';'C3S';'C3V'];
headers =
{'filename','mat_c_num','mat_c_mean','mat_c_sd','mat_i_num','mat_i_m
ean','mat_i_sd','mat_NR',...

'non_c_num','non_c_mean','non_c_sd','non_i_num','non_i_mean','non_i_
sd','non_NR'};
C1S = headers;
C1V = headers;
C2S = headers;
C2V = headers;
C3S = headers;
C3V = headers;

for i = 1:6:length(files);
    save_count = save_count + 1;
for j = 0:5
    count_6 = 1:6;
    a=[pth '\' files{i+j}];
    fid=fopen(a);
    t = textscan(fid, '%*f %f %*f %*f %*f
%f','headerlines',1,'delimiter','tab','emptyValue',0);
%                       1  2   3   4   5  6

    mat_c = []; mat_ca = 0;
    mat_i = []; mat_ia = 0;
    non_c = []; non_ca = 0;
    non_i = []; non_ia = 0;
    mat_noresponse = 0;
    non_noresponse = 0;

    for k = 1:length(t{1,1});
```

```
        if t{1,1}(k) == 8;
            if t{1,1}(k+1) == 16;
                mat_ca = mat_ca +1 ;
                mat_c(mat_ca) = (t{1,2}(k+1) - t{1,2}(k));
            elseif t{1,1}(k+1) == 17;
                mat_ia = mat_ia +1 ;
                mat_i(mat_ia) = (t{1,2}(k+1) - t{1,2}(k));
            else
                mat_noresponse = mat_noresponse + 1;
            end

        elseif t{1,1}(k) == 9;
            if t{1,1}(k+1) == 16;
                non_ia = non_ia +1 ;
                non_i(non_ia) = (t{1,2}(k+1) - t{1,2}(k));
            elseif t{1,1}(k+1) == 17;
                non_ca = non_ca +1 ;
                non_c(non_ca) = (t{1,2}(k+1) - t{1,2}(k));
            else
                non_noresponse = mat_noresponse + 1;
            end
        end
    end

    onerowinfo =
{files(i+j),mat_ca,mean(mat_c),std(mat_c),mat_ia,mean(mat_i),std(mat
_i),mat_noresponse...

,non_ca,mean(non_c),std(non_c),non_ia,mean(non_i),std(non_i),non_nor
esponse};

    save_name =
strcat([names(j+1,:),'(save_count,:)','=','onerowinfo;']);
    eval(save_name);


end
end

%%---Run_1_Fads_Day_1_Use_Delete_Rej_Sweeps_ASCI_from_Neuroscan

[filename,pathname]=uigetfile('*.*', 'Select A Data File','*.dat');
a=[pathname filename];
eventfile=a;
[cont_eeg_file,numSamples,numEpoc,Sf] = eeg32_cnt_2_Ch(eventfile);

 F3=cont_eeg_file(:,1);
 F4=cont_eeg_file(:,2);

 for i=1:numEpoc,
    low=1+numSamples*(i-1);
    high=numSamples*i;
    F3_epoc(:,i)=F3(low:high,:);
    F4_epoc(:,i)=F4(low:high,:);
 end
```

```
  for i=1:numEpoc

[psd_F3_epoc(:,i),F]=pwelch(F3_epoc(:,i),hamming(Sf),[],[],Sf);
      log_alpha_pwr_F3_epoc(i)=log(sum(psd_F3_epoc(9:14,i)));

[psd_F4_epoc(:,i),F]=pwelch(F4_epoc(:,i),hamming(Sf),[],[],Sf);
      log_alpha_pwr_F4_epoc(i)=log(sum(psd_F4_epoc(9:14,i)));
  end

  Fads=log_alpha_pwr_F4_epoc-log_alpha_pwr_F3_epoc;
  B_L_Fads=mean(Fads);
  varFads=std(Fads);

     [sort_epocs,ind_epocs]=sort(Fads,(2),'descend');  % Sorts
Frontal Asymmetry scores with their values and indices

  epocs_mat=[sort_epocs' ind_epocs'];                % Makes a 2
column matrix with epoch asym scores on left & index on right

    Hiten= [epocs_mat(1:10,:)];
    Lowten=[epocs_mat(numEpoc-9:numEpoc,:)];

   HiMean=mean(Hiten(:,1));
   LowMean=mean(Lowten(:,1));

Fads_mtrx_indx_D2_BL(1,1) = {filename(1,1:9)};  % Note squiggly
brackets of Cell Matrix
Fads_mtrx_indx_D2_BL(1,2) = {B_L_Fads};
Fads_mtrx_indx_D2_BL(1,3) = {varFads};
Fads_mtrx_indx_D2_BL(1,4) = {HiMean};
Fads_mtrx_indx_D2_BL(1,5) = {LowMean};



  [MaxFads,Indmax]=max(Fads);
  [MinFads,Indmin]=min(Fads);
  no_pos_epocs=length(find(Fads>0));  % This gives the # of positive
epochs
  no_neg_epocs=length(find(Fads<0));
  %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
 for i =1:numEpoc
  alpha_pwr_F3_epoc(i)=sum(psd_F3_epoc(9:14,i));
  alpha_pwr_F4_epoc(i)=sum(psd_F4_epoc(9:14,i));

  alpha_5_pwr_F3_epoc(i)=sum(psd_F3_epoc(9:14,i)/5);
  alpha_5_pwr_F4_epoc(i)=sum(psd_F4_epoc(9:14,i)/5);

   Mean_F3_alpha_pwr=mean(alpha_pwr_F3_epoc);
   Mean_F4_alpha_pwr=mean(alpha_pwr_F4_epoc);
 MeanNorm_F3_alpha_pwr=mean(alpha_5_pwr_F3_epoc);
MeanNorm_F4_alpha_pwr=mean(alpha_5_pwr_F4_epoc);
 end
```

```
Mean_F3_epoc=mean(F3_epoc,2); % If want to plot
Mean_F4_epoc=mean(F4_epoc,2);

figure(1)
plot(Mean_F3_epoc); hold on
plot(Mean_F4_epoc,'r');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%
  [sort_epocs,ind_epocs]=sort(Fads,(2),'descend');  % Sorts Frontal
Asymmetry scores with their values and indices

  epocs_mat=[sort_epocs' ind_epocs'];                % Makes a 2
column matrix with epoch asym scores on left & index on right

Hi_Low=[epocs_mat(1,:); epocs_mat(2,:); epocs_mat(3,:);
% Gives matrix of 3 highest & lowest scores
        epocs_mat(numEpoc,:); epocs_mat(numEpoc-1,:);
epocs_mat(numEpoc-2,:)];   % Just chose which second or epoch index
and plot that


 [sort_epocs,ind_epocs]=sort(Fads,(2),'descend');  % Sorts Frontal
Asymmetry scores with their values and indices

  epocs_mat=[sort_epocs' ind_epocs'];                % Makes a 2
column matrix with epoch asym scores on left & index on right



    Hiten= [epocs_mat(1:10,:)];
% as shown below
    Lowten=[epocs_mat(numEpoc-9:numEpoc,:)];

   HiMean=mean(Hiten(:,1))
   LowMean=mean(Lowten(:,1))
```

Appendix IV: LabVIEW Diagram



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