THE RELATIONSHIP BETWEEN MEMORY AND EVENT-RELATED POTENTIALS IN PATHOLOGICALLY IMPULSIVE AGGRESSIVE JUVENILES: A RETROSPECTIVE CHART STUDY

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DEDICATION PAGE

This thesis manuscript is dedicated to my parents, Dr. Larry & Jere Fisher. Their limitless guidance, support, and love made this work possible.

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ABSTRACT

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This study is a retrospective chart review designed to test the Limbic Dysmodulation Hypothesis (LDH) of the etiology of impulsive aggression among 80 juveniles in residential treatment. The LDH suggests that limbic electrical dysfunction is the central cause of pathologically impulsive aggression. Specifically, abnormal electrical activity, or limbic kindling, is thought to lower the threshold for impulsive aggression. Thus, according to the LDH, neurophysiological indices of brain function (e.g., Event Related Potentials, ERPs) and

psychometric tests of limbic function (e.g., measures of memory) should be correlated among individuals with impulsive aggression. Variables of interest included age, gender, auditory ERPs (normal or abnormal), visual ERPs (normal or abnormal), and verbal and visual memory (indexed via the Wide Range Assessment of Memory and Learning, WRAML-2). In addition, verbal comprehension, perceptual reasoning and intelligence were measured using the Wechsler Intelligence Scale (WISC-IV). Contrary to the LDH, results indicated that measures of memory did not significantly correlate with neuroelectric measures as derived from neurologists' reports. However, summary variables of absolute memory differences (verbal minus visual memory from the WRAML2) and any ERP abnormality (either auditory or visual) were significantly positively correlated. Taken together, these findings suggest that although there is some relationship between memory and neuroelectric activity among impulsive aggressive juveniles, this relationship does not account for a substantial amount of the model variance. The LDH is not supported by these limited findings.

CHAPTER 1

INTRODUCTION

The current project was designed to investigate a potentially neurobiological etiology of impulsive aggression. Specifically, this study focused on a possible electrical condition of the brain (e.g., limbic kindling) hypothesized to cause pathological forms of impulsive aggression in juveniles. This area of research is important, as the assessment, treatment and management of aggressive youth represents a major clinical challenge facing pediatric mental health professionals today (Connor, 2002). The scope of this problem is daunting, as aggression is reported to be the principal reason for psychiatric hospital admissions among juveniles (Volavka, 2002). Currently, no nationally representative survey of pediatric mental health treatment centers exists to reveal data on rates of aggression among clinically referred youth. However, smaller, single site studies suggest that aggressive behavior is prevalent, occurring in lifetime rates of 50-90% among psychiatrically referred juveniles, ages 5-19 (Connor et al., 1997; Fritsch et al., 1992). Further, although data are not readily available for juveniles, Coccaro and colleagues (2004) report that the incidence of Intermittent Explosive Disorder (IED, a disorder categorized by outbursts of impulsive aggression) may be as high as 11.1% in lifetime prevalence and 3.2% 1-month prevalence, in a community sample of 253 adults (Coccaro et al., 2004).

Scientific research in the area of aggression is multifactorial, interdisciplinary and complex. The quest to understand human aggression has a long and rich history. Great thinkers such as Aristotle, Hippocrates, Plato, Locke, Rousseau, and Freud have all attempted to examine and explain this behavioral phenomenon (Coccaro, 2003). This chapter will review the definition, history and theories of aggression, as well as more recent theories differentiating the underlying mechanisms of premeditated and impulsive aggression.

Definitions

To appreciate the research literature of this area, one must first define aggression. Aggression is defined as, "overt behavior that has the intention of inflicting harm to another individual" (Moyer, 1971). As this definition illustrates, aggression is a complex behavior with social aspects, as well as assumptions regarding the 'intention' of the perpetrator. Aggressive behavior has evolved to overcome competition for resources and to defend the individual against attack (Berkowitz, 1993). Aggression may result whenever the interests of two individuals conflict, or when motivated behavior is frustrated. Aggression is generally a normal adaptive behavior, although potentially dangerous. It can also be disruptive to the interpersonal relationships of social animals. When aggression occurs with little or no provocation, or when it occurs with exaggerated severity, significant frequency, or is out of its social context, such aggression is defined in psychiatry as 'pathological' (Nelson & Trainor, 2007). In the justice system, aggression characterized in this manner would be called 'violence'. More recently, aggression has been described as, "…any form of a behavior directed towards the goal of harming another person who is motivated to avoid such treatment" (Coccaro, 2003).

Persistent aggression can be a social, psychological, or biological problem. A hair-trigger temper can be related to a neurophysiological issue (Volavka, 1995), a chemical imbalance in the brain (e.g., Bipolar Disorder), or a psychological problem such as hostility (Coccaro, 2003). While aggression can be adaptive (e.g. when employed for self-defense), it is considered maladaptive when it becomes repetitive, severe, socially disruptive, or when there is little or no provocation.

Historical Theories of Aggression

Sigmund Freud, in his book, *Jenseits des Lustprinzips [Beyond the Pleasure Principle]*, posited that all humans have an instinctive "death drive" (1920, English translation in 1922). Freud further suggested that the "restriction of the instincts" was causally connected to aggression. Thus, according to Freud, our innate death wish denied by the state, or the church, creates a restriction of an instinctual death wish, which then translates into aggression. Another early hypothesis, the Frustration-Aggression Hypothesis, assumed that "…the occurrence of aggression always presupposes the existence of frustration and, contrariwise, that the existence of aggression always leads to some form of aggression" (Miller, 1941). A conceptualization of this theory might be that humans are motivated to remove obstacles from their goals. Aggression is often an effective method of removing such obstacles. The Social-Learning Theory is another concept of historical interest in the study of aggression. This theory posits that an individual learns aggressive behavior by modeling observed behavior or by social reinforcement (Bandura, 1962).

Recent Theories of Aggression

More recently, the Psychobiological Theory of Aggression proposed by Mark Hillbrand (1994), suggests that aggression is a function of psychobiological forces that provide an evolutionary advantage for humans who engage in aggressive behavior. For example, in humans and other primates, males perpetrate a large proportion of aggression in order to compete for females in their territory. A related literature suggests that the actions of increased testosterone in males lead to a decrease in the threshold for physical aggression (Archer, 1988), thus providing a competitive advantage when seeking a mate.

The Arousal Theory is another relatively recent theory in the study of human aggression (Venables, 1988). This theory states that aggressive violence is caused by either sub-cortical under-arousal (e.g., antisocial personality or psychopathy) or cerebral hyper-arousal (e.g., Bipolar Disorder or Intermittent Explosive Disorder). Venables (1988) describes a concept of "vagotonia" which suggests that some antisocial individuals who have a predisposition for violent behavior also have an autonomic nervous system that favors parasympathetic as opposed to sympathetic processes. Such a predisposition would result in autonomic under-arousal and "fearlessness". In psychopathic or antisocial individuals, this factor may be mediated by sensation-seeking behavior. For instance, drug seeking or criminal behavior may increase arousal, which counteracts the theorized cortical under-arousal (Venables, 1988). These behaviors, in turn, are frequently linked to violence (Venables, 1988).

Animal models of aggression have yielded a number of behavioral subtypes as described by Moyer (1967). Operationally defined subtypes include the following: fear

-induced aggression, maternal aggression, inter-male aggression, irritable aggression, predatory aggression, territorial aggression and instrumental aggression. Fear-induced aggression is defensive, with behaviors aimed to escape a threat. Maternal aggression is defined as aggression against intruders and/or behavior designed to protect their young. Inter-male aggression is defined as a fight for social dominance. Irritable aggression is a response to pain or deprivation. Predatory aggression's aim is to kill and consume prey, typically that of a different species. Territorial aggression is a type which Moyer defined as resident-intruder aggression. Irritable aggression was Moyer's final aggression subtype, described as aggression that is shaped or reinforced by irritations or frustrations (Moyer, 1967).

In contrast to animal studies, aggressive subtypes proposed for humans are usually dichotomous (McEllistrem, 2002). For instance, research concerning maladaptive human aggression often makes a distinction between premeditated (cold-blooded, predatory, or proactive) aggression and impulsive (hot-tempered, affective, or reactive) aggression (Conner, 2002). Impulsive aggression is more emotional, and is considered to be more biological in origin (McEllistrem, 2002). Premeditated aggression is considered an instrumental, purposeful, controlled aggressive behavior and may be more likely to be learned or influenced by psychosocial factors (Stanford et al., 2003). The level of behavioral control has been described as the key distinction between premeditated and impulsive aggression (Stanford, et al., 2005), with premeditated aggression being more "in-control" and impulsive aggression being more "out-of-control". Impulsive aggression has specifically been identified as having a number of neurologic deficits that could affect an individual's ability to process and react to eliciting

stimuli (Barrat, Stanford, Kent & Felthous, 1997; Houston & Stanford, 2001; Raine et al., 1998; Stanford et al., 2003). Research suggests that impulsive aggression is a distinct subtype of aggression (Coccaro, 2003). Although the terminology associated with human aggression may vary in the literature (e.g., impulsive versus premeditated, affective versus predatory, reactive versus instrumental, etc.), all dichotomous terms describe similar concepts. One subtype is cold-blooded, in- control, purposeful, and more psychosocial in origin, while the other subtype is hot-tempered, out-of-control, impulsive, and more biological in origin (McEllistren, 2002).

There are a number of supported etiological theories of impulsive aggression. It is suggested that impulsive aggression has more neurobiological than psychosocial underpinnings (Slever, 2002). Additionally, from an evolutionary perspective, impulsive aggression may be characterized across a variety of species as a response to a potential threat and appears to be an inborn response (Slever, 2002). Furthermore, recent genetic research has linked DNA polymorphisms of the dopaminergic system to pathological aggressive behavior (Chen et al., 2007; Guo, Roettger, & Shih, 2006). In addition, twin studies also suggest a substantial genetic component to impulsive aggression (Coccaro, 1997). At the time of this review, the neurobiological model of impulsive aggression has attracted the greatest amount of research, and as such, is the best supported of the etiological theories.

Recent literature suggests that two factors exist within the subtypes of impulsive aggression. The Two-Factor Neurobiological Model of impulsive aggression focuses on emotion-control versus impulse-control (Coccaro, 2003). The first factor, emotion-control, involves the sub-cortical, temporal-limbic regions of the brain, abnormalities of

which may manifest behaviorally as explosive temper, or extreme emotional outbursts (Best, 2002; Coccaro, 2006; Coccaro, 2007). In other words, patients with such conditions may exhibhit *too much emotion*. The second factor, impulse-control involves the prefrontal regions of the brain, abnormalities of which may manifest behaviorally as symptoms of impulsivity and the failure to inhibit reactions when it would be appropriate to do so (Best, Williams & Coccaro, 2002). In other words, this second factor suggests *too little control* of impulse behavior. Studies involving patients with lesions to the orbital prefrontal cortex and anatomically connected areas including the amygdale and other limbic structures have provided insight into the neurobiological underpinnings of impulsive aggression (Best, 2002). Lesions to these areas may cause patients to develop impulsive or explosive aggression, to show little control over their emotions, and to be unaware of the implications of their actions (Best, 2002). On the basis of lesion studies, it is hypothesized that patients who suffer from impulsive or explosive aggression share a similar locus of neuroanatomical disruption (Best, 2002). This is consistent with the two-factor model described above, with emotion-control problems being linked to impairments in the limbic system (e.g., hair trigger temper, explosive emotions), and impulse-control problems being linked to impairments in the prefrontal cortex (e.g., impulsive, uninhibited reaction). Mechanisms involved in limbic and prefrontal hypotheses are illustrated in Figure 1.

Further, recent research points to neurochemical abnormalities in impulsive aggression, with many studies demonstrating the importance of serotonin levels in the brain (Goveas, 2004). In general, studies of serotonin metabolites in patients with impulsive aggression show an inverse relationship between levels of serotonin and levels

of aggression (Coccaro, 1996). Aggressive behavior is also related to the action of dopamine in the frontal lobe of the brain with low dopamine associated with more impulsive behaviors (Rodriguiz, Chu, Caron, & Wetsel, 2004).

Neural imaging studies of murderers, psychopaths, and habitual criminals have suggested more *normal* frontal lobe function in premeditated criminal behavior but more frontal *dysfunction* in impulsive crimes of passion (McEllistrem, 2004; Raine, 1993). Recently, a study employing functional magnetic resonance imaging (fMRI) during a well-validated facial emotion processing task, suggested a putative link between amygdala function and impulsive aggression (Coccaro, 2007). Results indicated that, among patients showing impulsive aggression, there was significant threat-related amygdala hyperactivity. This adds additional evidence in support of a link between a dysfunctional limbic system and pathological impulsive aggression. Furthermore, similar relationships between neurobiological issues and impulsive aggression have been noted in studies of brain electrical activity. For example, increased inter-ictal irritability and impulsive aggression have been noted in temporal-limbic epilepsy (Spears, Schomer, Blume, & Mesulan, 1985). Also consistent with a neurobiological focus, a large number of studies have shown a relationship between electroencephalographic (EEG) abnormalities and impulsive aggression (Stein, Towey & Hollander, 1995).

Although the studies reviewed above approach aggression from different angles, use different populations, and examine different species, all converge on a similar conclusion. Namely, that the etiology of impulsive aggression, even in a normal population, is more likely to be biological rather than psychosocial and may involve a neurological network linking the functions of the limbic system (in the control of

emotions) and the functions of the prefrontal cortex (in the control of impulsive behavior). Thus, the etiology of most pathological forms of impulsive aggression may also be neurobiological, involving dysfunction in limbic and prefrontal brain regions. In summary, the general trend of recent research into the etiology of impulsive aggression suggests that both normal and pathological forms of impulsive aggression may be dependent upon the cortico-limbic network. Defects in the genetic, chemical, electrical, or structural systems related to this network may result in pathological aggression. With limbic dysfunction, patients may exhibit an over-reactive emotion system; whereas, with prefrontal lobe dysfunction, there may be an under-reactive impulse control system. Therefore, either type of dysfunction may result in pathologically impulsive aggression. This conclusion does not deny that aggression involves many factors, including psychosocial factors; however, with regard to pathologically impulsive aggression etiology is believed to be primarily neurobiological in nature.

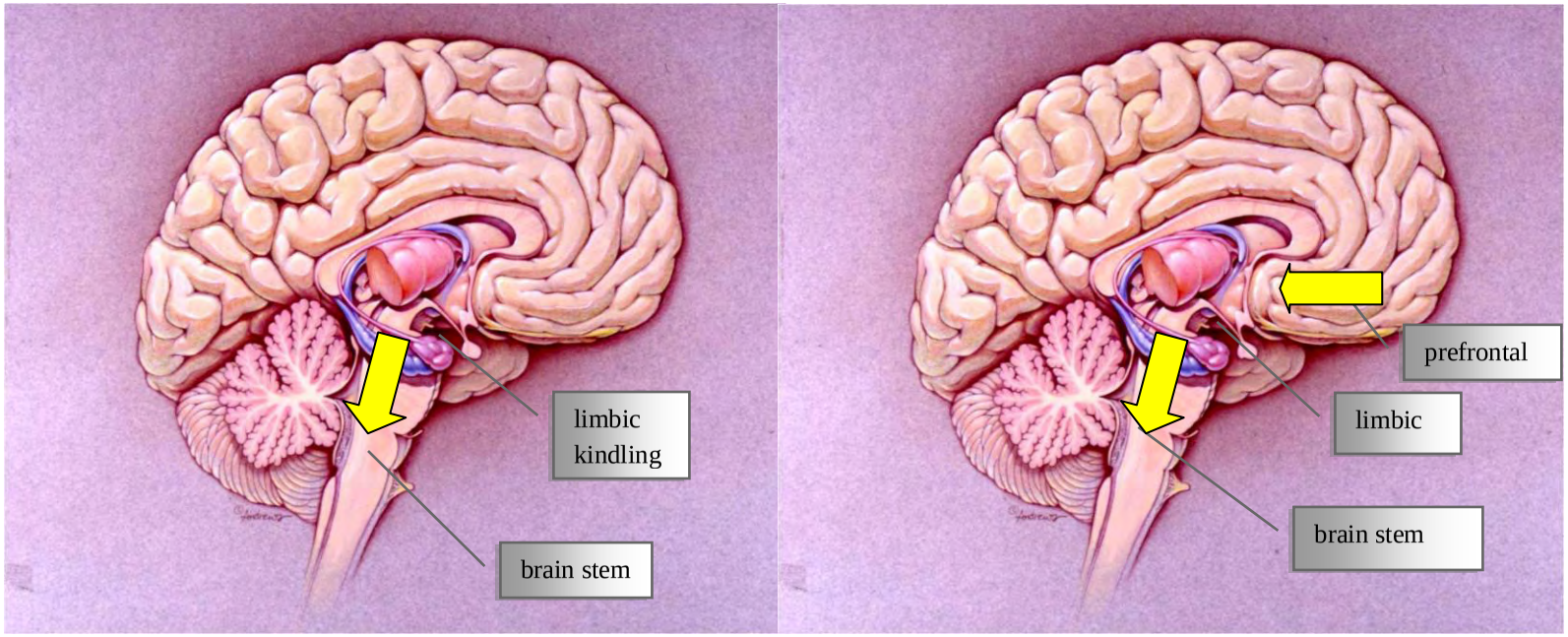

Figure 1. The Limbic Dysmodulation Hypothesis (left) versus the Prefrontal Dysfunction Theory (right). Figure used with kind permission of UHS Neurobehavioral Systems, Inc.

CHAPTER 2

THE LIMBIC DYSMODULATION HYPOTHESIS

Some juvenile patients admitted for aggressive outbursts have been found to have a combination of psychiatric disorders and brain abnormalities; in fact, the field of clinical neuropsychiatry, a relatively new branch of medicine, has been established to serve this population (Coffey, Brumbeck, Rosenberg & Voeller, 2006). In clinical neuropsychiatry, there is a relatively recent hypothesis, the Limbic Dysmodulation Hypothesis (LDH), which suggests that impulsive aggressive outbursts in juveniles are the result of an electrical disorder within the limbic area of the brain (Matthews, Fisher & Seals, 2001). This electrical disorder of the limbic system could lead to extreme emotions, with a lowering of the threshold for aggressive behavior. The theorized electrical disorder is referred to as "limbic kindling", as described by Kraus (2000), which means that impulsive aggression is not a form of epilepsy but, rather, an increased neuronal sensitization. This type of limbic kindling, or electrical sensitization in the limbic areas of the brain, refers to the development of an exaggerated response to a stimulus that was previously "sub-threshold". The term "sub-threshold" means that the stimulus did not originally elicit aggression, but that after limbic kindling has developed the stimulus is no longer innocuous and will now trigger aggression. In clinical terms, it means that a juvenile who develops limbic kindling may subsequently show impulsive or explosive aggression to minor provocations that previously would have been innocuous.

According to the LDH, it is because of this limbic electrical disorder that such juveniles become hypersensitive to trivial provocations and show persistent impulsive aggression that may become pathological (e.g., too severe, too frequent, and out of proportion to the provocation). Frequently, pathologically impulsive aggression leads to eventual psychiatric hospitalization or placement in a psychiatric residential treatment center.

The LDH suggests that pathological aggression is due to an early (prenatal or perinatal) brain disorder that later develops into a limbic electrical disorder (e.g., limbic kindling), which may be evaluated in clinical practice by recording of Event Related Potentials (ERPs) in response to auditory or visual stimuli. According to the LDH, excessive amplitude of long latency (500 millisecond) ERPs are the optimal means of measuring sensitization of the limbic system, assuming a subcortical origin for neuroelectric activity within the brain. In a population of pathologically aggressive juveniles, a study by Fisher and colleagues (2008) demonstrated that 91.5 % of participants showed abnormally large amplitudes in the auditory ERP, the visual ERP, or both. These findings are consistent with the LDH's suggestion that that the ERP may be sensitive to the electrical abnormalities associated with juvenile pathological aggression. Further, because the hippocampus, important for memory, is also a part of the limbic system, the LDH has suggested that the electrical over-arousal, or kindling, of the limbic system would cause impairment in memory.

To summarize, the LDH (Matthews, Fisher, & Seals, 2001) as it applies to the current study, posits the following: (1) Prenatal or perinatal brain disorders, such as a difficult delivery or oxygen deprivation at birth, can produce later electrical sensitization

of the brain in the form of limbic kindling. (2) As a consequence of limbic kindling, emotions can become extreme, resulting in a lowering of the threshold for pathologically aggressive reactions. (3) The result is out-of-control, impulsive aggression, or prolonged explosive rage outbursts, accompanied by impairment of memory for the aggressive event. (4) Long Latency (500 millisecond), auditory or visually stimulated Event Related Potentials (ERPs) are the best method of measuring these electrical abnormalities of the brain

The present study is a preliminary investigation of the LDH's prediction that the limbic system is the primary region associated with pathological aggression in juveniles. Based on LDH suggestions, if there is an electrical disturbance of the limbic system that contributes to pathological aggression, then one might expect impairment not only in electrical function, (e.g., abnormal ERPs), but also some abnormality in memory (e.g., abnormal memory scores on a psychometric test). The hippocampus, a component of the limbic system, is associated with verbal and visual memory (Yudofsky & Kim, 2004). Therefore, based on the LDH, the current study hypothesized that, for a population of pathologically aggressive youth, abnormalities in psychometric measures of verbal and visual memory would be correlated with abnormalities in long latency (500 millisecond) auditory and visual ERPs.

CHAPTER 3

ELECTROENCEPHALOGRAPHY, EVENT RELATED POTENTIALS & MEMORY

Electroencephalography (EEG) is a relatively inexpensive, noninvasive method that has shown benefit in identifying electrophysiological abnormalities in many psychiatric conditions (Yudofsky & Kim, 2004). EEG measures the summed synaptic potentials of the electrical activity of the brain as recorded using external scalp electrodes (Kandel, Schwartz & Jessel, 2000). However, standard EEG, as a method of measuring electrical activity of the brain, lacks information regarding spatial specificity of the source of the electrical activity recorded at the scalp. Further, for the population of impulsive-aggressive adolescents, the baseline EEG has been shown to be relatively insensitive to subtle brain dysfunction, as up to 85 percent of impulsively aggressive juveniles are reported to show normal EEG's in pediatric neurologists' reports (Fisher et al., 2008).

The ERP is a measure of the brain's electrical response to stimulation. It is derived from the EEG by averaging signals that have been time-locked to a given stimulus over 50-100 trials in order to improve the signal to noise ratio (Yudofsky & Kim, 2004). The ERP reflects different levels of information processing which occur as the rhythmic neuroelectric signals of the brain travel through the ascending activating system from the brain stem, past the limbic system, to the cortex (Kandel, Schwartz & Jessel, 2000). The ERP signal emerges as well-defined negative and positive peaks (e.g.,

N100, N200, P100, P200, P300, etc.) corresponding to neuroelectric responses of the brain in the milliseconds following stimulus presentation. For instance, according to Connor (2002), the first 100 milliseconds of ERP signal may correspond with very basic brainstem activity; whereas, the next two to three hundred milliseconds of ERP signal may correspond to limbic processing, and the next stage of 300-500 milliseconds following stimulus presentation may correspond to cortical perceptual and cognitive processing. Using the negative components as an example, the N100 (e.g., negative peak 100 milliseconds following stimulus presentation) reflects processing of simple sensory parameters of the stimulus (intensity, duration, complexity), while the N200 may reflect response inhibition (the opposite of impulsivity), and the N400 reflects higher level linguistic and semantic processing.

Magnetoencephalography (MEG) studies have shown that the source localization associated with an ERP can be linked to brain structures from the brain stem to the cortex (Wong, 1991). Unlike the EEG, the MEG is not distorted by the skull and can be used to demonstrate source localization for the electrical activity that is recorded at the scalp (Wong, 1991). As shown in Figure 2, the MEG suggests that the first 100 milliseconds post-stimulus is associated with ERPs originating in the brain stem and thalamus. From 100 to 300 milliseconds post-stimulus, ERPs may originate in the limbic system. From 300 to 500 milliseconds (and beyond), ERPs may have primarily cortical sources. Several additional studies have confirmed a limbic source for ERPs occurring 100 to 300 milliseconds post-stimulus. For instance, an MEG study by Okada and colleagues (1983) found that an “analysis of the pattern of the magnetic field showed that sources of the N200 and P300 lay deep in the brain, within the hippocampal formation”. Also, utilizing

auditory ERPs with surgically-implanted, intra-cranial depth electrodes, Halgren and colleagues (1992) found that auditory ERPs occurring between 100 and 300 milliseconds originated from the limbic region.

Memory

The LDH stipulates that the electrical abnormality (limbic kindling) associated with pathologically impulsive aggression is generated in the limbic system. Home to structures such as the hippocampus, the limbic system is the major anatomical area proposed to be involved in memory. Psychometric measures of memory, such as the Wide Range Assessment of Memory and Learning (WRAML 2), have been reported to be indicators of limbic functioning (Lezak, Howieson & Loring, 2004). Based on the LDH, the current study hypothesizes that abnormal electrical phenomenon in the limbic region may be related to functional deficits in memory systems.

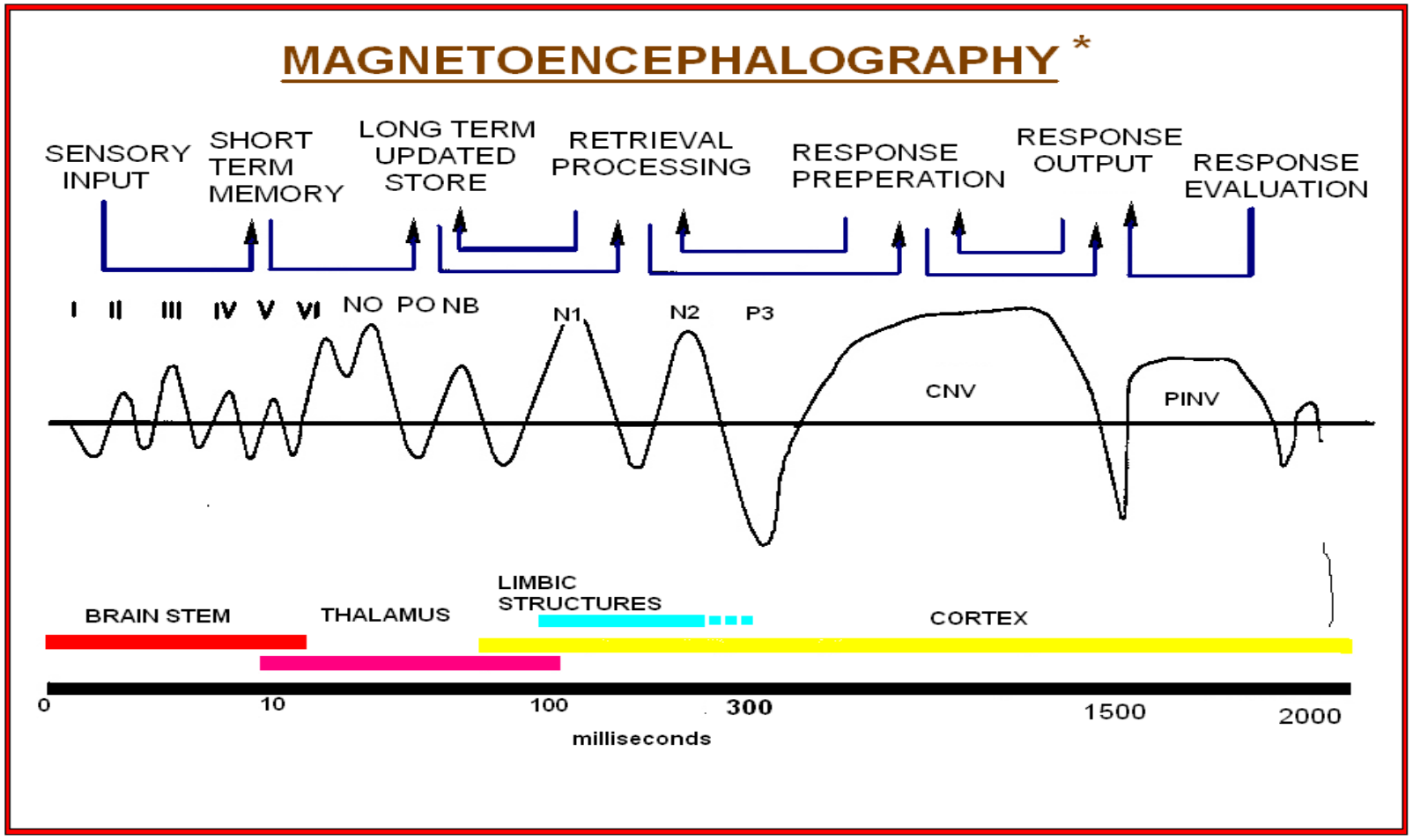

Figure 2. Magnetoencephalography & Source Localization of Event Related Potentials. Figure taken from *Introduction to Brain Topography*, by Peter K. H. Wong (Plenum Press, New York, 1991). Chart reprinted with kind permission of Springer Science and Business Media.

CHAPTER 4

STUDY HYPOTHESES

This study was designed as a preliminary investigation of the LDH. To this end, the study attempted to ascertain whether or not performance on tests of memory, obtained from the Wide Range Assessment of Memory and Learning (WRAML 2) would correlate with results of neurophysiological measures of the limbic system, as obtained from Event-Related Potentials (ERPs). The specific variables of interest, which are explained in detail in the methods section, included the visual & verbal memory index scores on the WRAML 2, as well as results of visual and auditory ERPs rated as normal or abnormal based on neurologists' reports. More specifically, significant correlations were predicted between visual memory index scores and visual ERPs, visual memory index scores and auditory ERPs, verbal memory index scores and visual ERPs, verbal memory index scores and auditory ERPs.

Summary Variables.

In an effort to provide a more robust model, absolute memory differences were calculated to detect within-subject memory disparity. The absolute memory difference was defined as the size of the difference between the WRAML 2 verbal memory index and the WRAML 2 visual memory index, independent of the sign or direction of that difference. In this sample, it is possible that a participant may have verbal and visual

memory scores that are not abnormal relative to the WRAML 2 norms. However, a 15 point (one standard deviation) difference between verbal and visual scores would still be considered of clinical interest. For example, if the verbal memory score is 10 points below the norm average and the visual memory score is 10 points above the norm average, then relative to the norm, neither score would appear to be abnormal. However, the 20 point difference between the two scores would suggest an abnormal memory disparity.

An additional summary measure of ERP abnormality, the any abnormal ERP variable, was also added based on current clinical use of ERP data at the residential treatment facility where data were collected. The variable, any ERP abnormality (positive vs. negative) is defined by the presence of abnormalities (or a lack thereof) in visual ERPs, auditory ERPs, or both. In clinical practice, such ERP data is used to select juvenile patients who are likely to respond to anticonvulsant medications designed to stabilize their pathologically impulsive aggression (Matthews et al., 2001). An abnormality in either visual ERP or auditory ERP, or both, is considered enough to predict a positive result for anticonvulsant medication. Thus, the summary variable of any abnormal ERP was included in the current study, and it was predicted that the absolute memory difference would be significantly correlated with any abnormal ERP.

CHAPTER 5

METHODS

Rationale

The present study is a review of the neuropsychiatric assessment data from the medical charts of pathologically aggressive juveniles who underwent treatment in a locked Residential Treatment Center (RTC) in central Texas. An RTC is a psychiatric facility devoted to treating juveniles with hard-to-treat psychiatric disorders. The most common reason for admission to this RTC is that the juvenile has shown impulsive or explosive aggression that is pathological (i.e., based on the RTC admission criteria, the aggression is out of proportion to the provocation, has caused severe injury to others, including bruising, bleeding, or broken bones, and the aggression has occurred three or more times in the prior 12 months). Also, these juveniles were unresponsive to prior outpatient treatments and/or acute hospitalizations and were considered to be in need of long-term (i.e., several months) treatment in a locked psychiatric facility. The assessment data collected at the start of treatment were used to help select medications and to design treatment plans. In this RTC, the assessment data included psychometric testing as well as neurophysiological testing. The availability of both memory tests (WRAMAL 2 verbal and visual memory scores) and ERP data (auditory and visual long latency ERPs) afforded a unique opportunity to compare the two types of brain measures in this clinically important population of pathologically aggressive juveniles.

RTC assessments were guided by the LDH. The neurologist who interpreted the neuroelectric testing (e.g., ERPs) indicated whether or not there was electrical abnormality in either temporal-limbic regions or frontal lobe regions. Similarly, psychomteric testing of the brain, reflecting activity of both brain areas, was conducted. The neuropsychologist who interpreted the data also reported any abnormality in temporal-limbic regions or frontal lobe regions. For the psychometric testing, the tests of memory are thought to reflect temporal limbic functioning and the tests of intellect are thought to reflect cortical and frontal lobe functioning. With this combination of data one can determine if there is a relationship between the psychometric and neuroelectric tests with regard to reported location of abnormality. Also, one can make a specific prediction that memory test scores, reflecting limbic system function, will predict ERPs associated with the temporal-limbic region. It is possible that a simple and inexpensive test of memory can predict the results of a more complicated and expensive electrical ERP test for impulsive-aggressive juveniles. The examination of these potentially predictive relationships is the focus of the current study.

Participants

Data were extracted from the medical records of 80 juvenile patients who had been admitted to an RTC in Central Texas for the treatment of pathological impulsive aggression. For admission to this RTC, the patient must have had several (at least 3) discrete episodes of failure to resist aggressive impulses that resulted in assaultive acts causing serious physical harm (i.e., with bruising, bleeding, or broken bones).

Additionally, the degree of aggression expressed during the episodes must have been grossly out of proportion to any precipitating psychosocial provocation. Also, for admission, the patients must have shown prior psychometric evidence of an intellect (e.g., IQ) of 70 or above. Excluded from admission were individuals who had severe language disorders (or did not speak English), were deaf, blind, or had severe mobility problems, suffered with severe medical illness (e.g., AIDS), were pregnant, had a history of arson, or had other conditions that could be a safety concern or would prevent them from participating in individual, group, and family psychotherapy.

Participants ranged in age from 6 to 17 years, with a mean age of 13 years. The participants were predominantly males (56 males and 24 females) and were predominately right hand dominant (74 right, 6 left). With few exceptions, the participants were Caucasian, and self-reported their state of residence as either Texas or California. Fifty percent of participants had completed 7th grade or higher.

For this population, psychiatric diagnoses determined upon admission to the RTC included Mood Disorder, Intermittent Explosive Disorder, and Attention Deficit Hyperactivity Disorder. Participants were excluded from further study if they had a diagnosis of Conduct Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, Pervasive Developmental Disorder, or any psychotic disorder not associated with a Mood Disorder. Also excluded were subjects whose aggressive behavior was considered to be a direct result of substance abuse or medication side effects. Lastly, subjects whose aggressive behavior may have been due to a general medical or neurological condition were excluded, unless the condition was prenatal or perinatal in origin and was considered chronic rather than progressive.

For the purposes of this study, the data extracted from medical records were cleared of all identifying information and patient privacy was protected using a coded number to represent the participant. Any datum that could be reasonably used to identify the patients was removed. Due to the retrospective nature of this study and the de-identified data, this study was found to be "exempt" by the Texas State Institutional Review Board, (Exemption #10-88320, March 10, 2008). Additionally, this study was reviewed and approved by the medical committee of the RTC where data were collected.

Neurophysiology (Event-Related Potentials)

Participants were seated in a comfortable chair in an electrically shielded room located in a quiet section of the RTC. The EEG was conducted by a trained EEG technician employed by the RTC, under the supervision of a licensed, board certified, neurologist (with specialty training as an electroencephalographer). The technician explained the procedure to the participant. The patient's head was measured and marked according to the International 10/20 System of Electrode Placement and 6 mm, Grass Gold EEG electrodes applied using standard technique (e.g., collodion, Grass paste/tape or electrode cap). The instrument was calibrated for a 50 microvolt signal (60 cycle filters off), 5 microvolts/millimeter sensitivity, high linear frequency filter of 70 Hz, and low frequency filter at 1.0 Hz, and the electrodes were checked for proper impedance (more than .5 k-Ohm and less than or equal to 5 k-Ohms). All ERPs were written digitally on a computer, and after processing and storage on backup CDs, were forwarded to a secure computer server from which an approved physician (with password control) could access the records (from a laptop computer that has been specially modified for this purpose). This server is maintained at the headquarter offices of Universal Health

Services (UHS) in King of Prussia, Pennsylvania. UHS is the parent company for the RTC housing the patient records used in this study. All digital computerized recordings, computers, CDs, and paper records are strictly maintained following all Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy regulations, as per the policy and procedures of UHS. Any paper records and CDs are kept under the supervision of a medical records librarian, who also follows all HIPPA privacy regulations.

In this RTC, auditory and visual ERPs were routinely conducted on juveniles admitted for pathologically impulsive aggression. The ERPs were long latency (500 millisecond) electrical responses time-locked to auditory (bilateral 86dB SPL, 1000 Hz tone, rise and fall time 10 milliseconds) or visual (Grass strobe light flash, 18 inches from closed eyes) stimuli, averaged from the background EEG over 100 trials. All stimuli were presented in random format with at least 1000 millisecond intervals. The test results were interpreted by a board certified pediatric neurologist (with specialty training as an electroencephalographer). The neurologist was blind to the participants' diagnoses (e.g., only participants' age and gender were given). The auditory and the visual ERPs consisted of averaged records taken from periods of artifact-free EEG. For each of the 20 electrodes, the raw records available to the neurologist consisted of a graph of the averaged ERPs, time locked from the moment of stimulation, with data points taken every 20 milliseconds for a total of 500 milliseconds. For each auditory and visual ERP, the neurologist had access to individual ERP graphs as well as to averaged graphs, which were computerized and compared to age- and gender-matched, proprietary norms provided by Cognitrace (e.g., manufacturers of the EEG machine) (Duffy, Burchfiel &

Lombroso, 1979). The following procedure was used: each point on the ERP graph was converted to a Z score, and these scores were used to create a normative ERP to compare to the participant's ERP. Norms provided from Cognitrace were based on 100 normal participants in each of the following age groups: five to seven, eight years, nine to thirteen, and 14 to 19. The use of these norms allowed the neurologist to employ an operational definition of amplitude abnormality by comparing the number of standard deviations by which a participant's ERP amplitude differed from the norm amplitude at specific points on the ERP waveform (e.g., P100, P200, P300, N100 and N200). The operational definition of abnormal referred to a condition in which participants' ERP wave amplitudes differed from the norm amplitude by at least 2.5 standard deviations. In this way, the amplitude and of the waveforms (auditory and visual) were considered normal or abnormal at each peak. However, if the amplitude of any of peak did not reach five microvolts in negative or positive amplitude, the ERP was considered absent and abnormal. Also, in terms of latency at each peak, the ERP was considered abnormal if the latency was early or late by 50 milliseconds or more (e.g., P300 would be considered abnormal if it occurred before 250 milliseconds or after 350 milliseconds). The neurologist reported the ERP abnormalities, using the standards described above, for auditory ERP and for visual ERP.

In addition, a summary variable was created, 'any ERP abnormality' (positive or negative), in which a participant with abnormality of auditory ERPs, visual ERPs, or both was counted as abnormal; that is "positive" for any ERP abnormality. This categorization scheme was similar to the clinical method used by the psychiatrists at the RTC, where any type of ERP abnormality reported by the neurologist (i.e., auditory ERP,

visual ERP, or both) was sufficient to predict that the participant would be a good candidate for consideration of anticonvulsant medication.

Psychometrics

In this RTC, tests of IQ and memory were routinely used as part of the assessment of juveniles admitted to the facility. The current study included data from the Wechsler Intelligence Scale for Children, fourth edition (WISC IV; Wechsler, 2003) and the Wide Range Assessment of Memory and Learning, second edition (WRAML 2; Sheslow & Adams, 2003). Only selected subtests of these psychometric instruments were employed in this study, including the WISC IV verbal comprehension index, perceptual reasoning index, and full scale IQ, and the WRAMAL 2 verbal memory index and visual memory index. According to the policy of the RTC, testing was not attempted until the participant was reported to be stable and cooperative enough for valid test results. For this reason, testing typically occurred several weeks after admission to the RTC. Testing was further delayed if there was any indication that the patient was ill or was experiencing sedation effects from medication. Testing was conducted in two segments, each approximately two hours in duration (depending on the number of breaks the subject needed). Participants were seated in a quiet room, devoid of distractions. Tests were conducted in the standardized manner as described in the instruction manuals for standardized tests.

Tests were conducted and scored by psychometric technicians, trained and supervised by a licensed psychologist, who was a full time employee of the RTC. A licensed psychologist interpreted and reported the results. The psychologists and the

psychometric technicians were familiar with and followed the American Psychological Association's published standards for educational and psychological testing. Internal consistency coefficients for the memory tests ranged from .82 to .96 for the index scores. The standardization sample is representative of the United States.

The WISC IV, published by PsychCorp, is a general intelligence test for ages 6 to 16 years. It is the newest version of the Wechsler series for children and adolescents. It yields a full scale IQ and four index scores: verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI). However, only the VCI and PRI were used for this study. Test re-test reliability for these scores is reported to be above .90 for all ages. The standardization sample is representative of the United States.

The WRAML 2, published by Psychological Assessment Resources, is a comprehensive evaluation of memory for ages 5 to 90 years. The test is individually administered. Although there are a six core subtests available, two primary summary scores were used for the current study: the verbal memory index and the visual memory index. The verbal memory index score is a measure of immediate verbal memory. The visual memory index score is a measure of immediate visual memory. An additional category, the 'absolute memory difference' (the verbal minus visual index difference, independent of direction of difference), was used as a measure of the memory disparity. This approach uses the participant as his or her own control using by comparing the disparity between that participant's verbal and visual memory. When working with a clinical population where abnormal scores on memory tests are common, the use of summary variables such as the absolute memory difference may be an important

alternative to comparing the participant to a normative database. In clinical populations, disparities within the same individual, (verbal versus visual memory index scores) are less common and may be a more robust tool for prediction. Creation of this variable was recommended by the licensed psychologists at the RTC.

Data Analysis Plan.

Data were analyzed using SPSS Version 17. Separate Pearson's correlations were conducted to test possible relationships between memory variables (visual, verbal and absolute difference) and ERP variables (normal vs. abnormal: auditory ERPs and visual ERPs; positive vs. negative: any ERP abnormality). Pearson's correlations were chosen to conduct analyses on variables of a dichotomous and continuous nature, as SPSS automatically incorporates the point-biserial method, appropriate for correlations of a mixed nature. See Table 1.

In addition, in an attempt to establish a predictive model built upon individual, significant correlations between memory and ERP variables, a secondary set of analyses were conducted using logistic regression. Background variables (IQ, age and gender) were examined for possible relationships with auditory and visual ERPs and any ERP abnormality using Pearson's correlations as described above. IQ, age and gender have been shown to influence ERP results, thus, these variables were entered as covariate predictors in logistic regression analyses (Hetrick et al., 1996; Jaušovec & Jaušovec, 2000; Juottonen, Revonsuo & Lang, 1996). IQ, age and gender were expected to share a significant proportion of variance within the statistical construct.

Table 1

Null Hypotheses of the Correlations

H_0	r=0	There is no relationship between the variables of Absolute Memory Difference and Any ERP abnormality.
H_1	r=0	There is no relationship between the Visual Memory Index on the WRAML2, & Any ERP Abnormality.
H_2	r=0	There is no relationship between the score on the Visual Memory Index on the WRAML2, & Visual ERP Abnormality.
H_3	r=0	There is no relationship between the score on the Visual Memory Index on the WRAML2, & Auditory ERP Abnormality.
H_4	r=0	There is no relationship between the score on the Verbal Memory Index on the WRAML2, & Any ERP Abnormality.
H_5	r=0	There is no relationship between the score on the Verbal Memory Index on the WRAML2, & Visual ERP Abnormality.
H_6	r=0	There is no relationship between the score on the Verbal Memory Index on the WRAML2, & Auditory ERP Abnormality.

Table 2

Null Hypotheses of the Logistic Regression

H_7	The full model with the six predictors, (Absolute Memory Difference, VCI, PRI, FSIQ, Age, Gender) against a constant-only model will not predict the presence or absence of Any ERP Abnormality.
H_8	Absolute Memory Difference does not predict group membership in Any ERP Abnormality.
H_9	Verbal Comprehension Index does not predict group membership in Any ERP Abnormality
H_{10}	Perceptual Reasoning Index does not predict group membership in Any ERP Abnormality.
H_{11}	Full-scale IQ does not predict group membership in Any ERP Abnormality.
H_{12}	Participant age does not predict group membership in Any ERP Abnormality.
H_{13}	Participant gender does not predict group membership in Any ERP Abnormality.

CHAPTER 6

RESULTS

Background characteristics of the participant sample are shown in Tables 3 and 4. The average age of participants was 13 years (M=12.84; SD=2,472; range=11). The sampled consisted of 56 males (70%) and 24 females (30%). The sample was predominately Caucasian, with Hispanic and African-American patients in the minority (exact ethnic breakdown unavailable). The average full scale IQ of the sample was 91.38 (SD=16.06; range=82). The average verbal memory of the sample was 83.77 (SD=14.45; range=64). The average visual memory score was 81.58 (SD=16.56; range=71).

Contrary to the LDH, no significant correlations were noted between auditory ERPs and verbal memory (r=.027, p=.82), auditory ERPs and visual memory (r=-.096, p=.43), auditory ERPs and absolute memory difference (r=.193, p=.11), visual ERPs and visual memory (r=-.016, p=.90), visual ERPs and verbal memory (r=.026, p=.83), and visual ERPs and absolute memory difference (r=.128, p=.30). See Table 5.

Interestingly, the summary variable of absolute memory difference was significantly correlated with the summary variable of any ERP abnormality (r=.236, p=.049), as shown in Table 5. Whereas this correlation may be statistically significant and may be useful for purely theoretical purposes, this finding may lack clinical significance, as it accounts for only 5% of the variance of the model. It should be noted

that neurologist analyses of ERP results were unavailable in 10 patient charts, thus the correlations were based on 70 cases.

Further analysis, using logistic regression with absolute memory difference, verbal comprehension index, perceptual reasoning index, full-scale IQ, age and gender as predictors of any ERP abnormality revealed the following. The model was significant (see Table 6); however, the model showed that only the variables of gender and absolute memory difference were statistically significant predictors. The variables of age, full scale IQ, VCI, and PRI were non-significant predictors.

Given the unequal distribution of positive and negative cases within the variable 'any ERP abnormality', it is important to consider the percentage of cases correctly predicted by the mode. For instance, the overall percentage (negative or positive for 'any ERP abnormality') of cases correctly predicted by the model was 84.3%. Further, 96.6% of cases of any ERP abnormality (positive) were correctly predicted based on the model. However, for cases designated as any ERP abnormality (negative), the model correctly predicted only 25% of the sample. Thus, the model has no real predictive utility. This situation is due to the high proportion of the sample that showed abnormality, as logistic regression is known to more effectively predict the larger proportion of the sample for statistically significant models.

Table 3

Demographics

N=80	
Age	6-17, Mean= 12.84, Std. Deviation= 2.472
Gender:	46 Male (70%), 24 Female (30%)
Grade:	1^{st}-11^{th}, Mean= 7.10, Std. Deviation= 2.374
Ethnicity	Predominately Caucasian – exact figures unknown to incomplete/missing data.
Geographic distribution	Patients from Texas & California predominately, exact figures unknown due to incomplete/missing data.

Table 4

Psychometrics

Wechsler Intelligence Scale for Children, Fourth Edition

	N	Range	Minimum	Maximum	Mean	Std. Deviation	Variance
WISC-IV VERBAL COMPREHENSION INDEX	80	77	54	131	91.95	15.890	252.504
WISC-IV PERCEPTUAL REASONING INDEX	80	75	58	133	92.64	16.222	263.145
WISC-IV FULL SCALE IQ INDEX	80	82	53	135	91.38	16.060	257.908
Valid N (listwise)	80						

Wide Range Assessment of Memory and Learning, Second Edition

	N	Range	Minimum	Maximum	Mean	Std. Deviation	Variance
WRAML VERBAL MEMORY INDEX	80	64	49	113	83.77	14.448	208.734
WRAML VISUAL MEMORY INDEX	80	71	45	116	81.58	16.556	274.096
Valid N (listwise)	80						

Table 5

Correlation Matrix

		PATIENT AGE	GENDER	VCI	PRI	FSIQ	WRAML2 VERBAL	WRAML2 VISUAL	ABSOLUTE MEMORY DIFFERENCE	AUDITORY EVOKED POTENTIALS	VISUAL EVOKED POTENTIALS	ANY ERP ABNORMALITY
PATIENT AGE	Pearson Correlation	1	.132	-.099	-.112	-.114	-.092	.058	.171	.098	.174	.196
	Sig. (2-tailed)		.243	.380	.324	.313	.418	.609	.129	.420	.153	.104
GENDER	Pearson Correlation	.132	1	-.107	-.083	-.120	.103	-.053	.149	-.084	-.038	-.216
	Sig. (2-tailed)	.243		.346	.462	.290	.362	.642	.186	.488	.754	.073
VCI	Pearson Correlation	-.099	-.107	1	.706	.929	.653	.502	-.185	-.085	.083	-.056
	Sig. (2-tailed)	.380	.346		.000	.000	.000	.000	.101	.484	.500	.644
PRI	Pearson Correlation	-.112	-.083	.706	1	.912	.472	.548	-.186	-.135	.047	-.079
	Sig. (2-tailed)	.324	.462	.000		.000	.000	.000	.099	.266	.704	.517
FSIQ	Pearson Correlation	-.114	-.120	.929**	.912**	1	.623**	.559**	-.209	-.107	.074	-.059
	Sig. (2-tailed)	.313	.290	.000	.000		.000	.000	.063	.377	.545	.628
WRAML2 VERBAL	Pearson Correlation	-.092	.103	.653	.472	.623	1	.487	.050	.027	.026	-.009
	Sig. (2-tailed)	.418	.362	.000	.000	.000		.000	.659	.824	.831	.944
WRAML2 VISUAL	Pearson Correlation	.058	-.053	.502**	.548**	.559**	.487**	1	-.098	-.096	-.016	-.020
	Sig. (2-tailed)	.609	.642	.000	.000	.000	.000		.387	.430	.899	.867
ABSOLUTE MEMORY DIFFERENCE	Pearson Correlation	.171	.149	-.185	-.186	-.209	.050	-.098	1	.193	.128	.236*
	Sig. (2-tailed)	.129	.186	.101	.099	.063	.659	.387		.109	.296	.049
AUDITORY EVOKED POTENTIALS	Pearson Correlation	.098	-.084	-.085	-.135	-.107	.027	-.096	.193	1	.331	.803
	Sig. (2-tailed)	.420	.488	.484	.266	.377	.824	.430	.109		.005	.000
VISUAL EVOKED POTENTIALS	Pearson Correlation	.174	-.038	.083	.047	.074	.026	-.016	.128	.331	1	.539
	Sig. (2-tailed)	.153	.754	.500	.704	.545	.831	.899	.296	.005		.000
ANY ERP ABNORMALITY	Pearson Correlation	.196	-.216	-.056	-.079	-.059	-.009	-.020	.236*	.803**	.539**	1
	Sig. (2-tailed)	.104	.073	.644	.517	.628	.944	.867	.049	.000	.000	

Table 6

Logistic Regression Analysis

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	13.469	6	.036
	Block	13.469	6	.036
	Model	13.469	6	.036

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	50.671	.175	.292

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	VCI	-.189	.137	1.920	1	.166	.828
	PRI	-.170	.121	1.955	1	.162	.844
	FSIQ	.324	.231	1.974	1	.160	1.382
	Age	.189	.142	1.757	1	.185	1.208
	Sex*	-1.576	.794	3.941	1	.047	.207
	ABSMEMDIFF*	.122	.060	4.223	1	.040	1.130
	Constant	3.657	3.755	.949	1	.330	38.756

a. Variable(s) entered on step 1: VCI, PRI, FSIQ, Age, Sex, ABSMEMDIFF.

\Table 6 (cont'd).

Logistic Regression Analysis

Correlation Matrix

		Constant	VCI	PRI	FSIQ	Age	Sex	ABSMEMDIFF
Step 1	Constant	1.000	-.548	-.483	.447	-.314	-.228	.092
	VCI	-.548	1.000	.913	-.971	-.083	-.079	-.277
	PRI	-.483	.913	1.000	-.973	-.082	-.138	-.296
	FSIQ	.447	-.971	-.973	1.000	.080	.125	.304
	Age	-.314	-.083	-.082	.080	1.000	-.140	-.126
	Sex	-.228	-.079	-.138	.125	-.140	1.000	-.243
	ABSMEMDIFF	.092	-.277	-.296	.304	-.126	-.243	1.000

CHAPTER 7

DISCUSSION

This study is unique in that it is the first formal research examination of a relatively new clinical hypothesis (e.g., the Limbic Dysmodulation Hypothesis, LDH) suggesting that limbic electrical dysfunction causes pathologically impulsive aggression in juveniles. Clinically, ERPs are used in neuropsychiatry to measure the presumed limbic electrical disorder. To date, however, there has been no study to support (or refute) the use of ERPs for this purpose. The current study is not a comprehensive test of the presumed neuroelectric disorders associated with impulsive aggression, but rather, it is a test of one specific prediction from the LDH. That is, if limbic electrical dysfunction explains the origin of pathological aggression in juveniles, as suggested by the LDH, then one would expect that different measures of limbic dysfunction would correlate statistically. According to the LDH, long latency auditory and visual ERPs are appropriate measures of limbic electrical dysfunction (e.g., limbic kindling). Psychometric measures of memory also reflect the function of the limbic system and, according to the LDH, these measures should correlate with long-latency ERPs in aggressive juvenile populations. In the current retrospective chart review study of this type of population, however, basic measures of verbal and visual memory (from the WRAML 2) did not significantly correlate with either visual or auditory ERPs as assessed by a neurologist. These results are contrary to the predictions of the LDH.

However, when analyzed via logistic regression, the summary variable of absolute memory difference showed statistical significance in predicting the summary variable of any ERP abnormality. While this finding was statistically significant, it may not be clinically important because it explained only a small percentage of the variance. Therefore, the predictive utility of this model was quite weak, leading to questions about the validity of the LDH. Numerous potential explanations exist. For instance, perhaps a limbic origin of this condition, as proposed by LDH, is not the case; perhaps the condition of pathologically impulsive aggression is not based on an electrical disorder; or, perhaps long latency ERPs are not valid measures of the hypothesized electrical disorder, or do not adequately reflect limbic dysfunction.

Therefore, one simple reason for this study's largely negative results might be that the LDH is incorrect and that limbic kindling, producing excessive electrical activity in the limbic system, is not the major etiology for pathological impulsive aggression in juveniles. One might speculate that if the LDH is wrong then perhaps prefrontal lobe dysfunction might be the major etiology (Best, Williams & Coccaro, 1992). However, there are many other logical explanations. For example, it is conceivable that the LDH proposal regarding limbic kindling is only true for females. Since the majority of the current sample was male, this could explain why the LDH prediction explained very little of the variance. This possibility could be tested by including larger numbers of female participants distributed more evenly within normal and abnormal ERP groups, a design that was beyond the scope of the current dataset.

Also, one could speculate that the LDH prediction could not explain much of the variance of the population at this RTC because this population had such a high percentage of ERP abnormalities. That is, the distribution of normal vs. abnormal ERPs was not evenly divided. Another explanation could be that LDH applies to only impulsive cases that are explosive; whereas, non-explosive cases may have a prefrontal origin. It can be speculated that a prefrontal origin for aggression applies to cases with both impulsive and premeditated aggression, but the LDH applies only to purely impulsive cases. Since recent hypotheses regarding prefrontal dysfunction in aggression were largely derived from studies of violent criminals, who might display both subtypes of aggression (Best, Williams & Coccaro, 1992), there might be some credence to this last speculation. Finally, predictions of the LDH depend on a degree of limbic dysfunction severe enough that both memory and ERP measures would be adversely affected. It is possible that the juveniles included in the current study did not have a limbic disorder with that level of severity. In any event, the current results do *not* suggest that memory scores can be used as a simple and less expensive measure (vs. ERP testing) for predicting neuroelectrical disorders of a limbic nature among aggressive juveniles.

The fact that this study provides so little support for the LDH raises a clinical question: Is the RTC's use of electrical ERP abnormality as a basis for selecting patients for anticonvulsant medication appropriate? For the most part, the use of anticonvulsant medication for treatment of pathological aggression is an 'off label' use, meaning that it is not an approved use by the Food & Drug Administration (FDA). However, there are studies that have shown benefits of using anticonvulsant medication in this population

(Stanford et al., 2005). However, the use of ERPs to select patients' medications is not an evidence-based approach since there have been no studies that have shown the efficacy of using ERPs for this purpose. Nonetheless, at the RTC where data for the current study were collected, anticonvulsant medications use is based solely on the LDH.

There are limitations in this study inherent in any retrospective study, such as lack of control of variables, lack of availability of records, and the quality and completeness of records. Also, as there was no random assignment to the intake of the residential treatment center, any circumstances (e.g. managed care, low socio-economic status) which might have precluded patients from being admitted to the treatment center could also impact the ecological validity of the results. Additionally, as the amplitude and latency data for individual ERPs were not available for study, the neurologists' reports in the medical records were the only basis for gauging the normality (e.g., normal vs. abnormal) of the visual and auditory ERPs. Future studies, including a more in-depth analysis of the amplitudes and latencies of individual ERPs might provide additional insight into the specific cognitive processes that may be compromised among juveniles with impulsive aggression. Based on the results of the current study, further investigation of the electrical activity of the frontal lobe of the brain and its relationship to impulsive-aggression (as an alternative to the LDH) may be warranted.

It is important to note that the current study does not represent a comprehensive test of the LDH; it merely presents the first challenge to this hypothesis. There may be reasons for this negative finding other than a conclusion that the LDH is incorrect. However, the results of the current study suggest four possible lines of future research. Firstly, a clinical study is recommended to examine the utility of using ERPs to predict

medication efficacy in pathologically aggressive juveniles. Secondly, further investigation into the 'limbic kindling' hypothesis is warranted, and fMRI might provide a more suitable and spatially superior method for examining subcortical brain dysfunction. Additionally, diffusion tensor imaging techniques could be employed to detect structural abnormalities in the limbic-prefrontal afferents and efferents, which might better explain the pathology of impulsive aggression in juveniles. Thirdly, the prefrontal hypothesis could be evaluated using ERP studies matched with psychometric testing of the frontal lobe. Fourth, as gender was a weakly predictive variable in the current study, the evaluation of electrical abnormalities (or lack thereof) in a larger group of male and female juveniles is warranted. A further retrospective study of this population measuring a broader range of cognitive functions and using a complete psychometric battery to examine the differences by gender would be useful. This would be a particularly beneficial contribution to the literature, which remains sparse with regard to gender-related studies of impulsive aggression.

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VITA

William Ira Fisher was born in New York, New York on September 17, 1971, the son of Dr. Larry Fisher and Jere Ann Fisher. After completing his high school education in Fargo, North Dakota at Woodrow High School in 1989, he joined the United States Navy. After service during Operation Desert Shield/Storm aboard the U.S.S. Carl Vinson CVN-70, he joined his family in Texas. He completed his Associates in Applied Science degree from the Texas Culinary Academy in 1996 and worked as a chef and in the wine business for several years. After deciding on a career-change, he began his studies in psychology at Texas State University-San Marcos. In 2006, he was awarded the Alexander Psychobiology/Psychophysiology Award from the Texas Psychological Foundation for his work entitled, "Youth with impulsive aggression: Anticonvulsant medication compliance and outcome for 2005-2006". This paper was published in abstract in the Journal of Neuropsychiatry and Clinical Neurosciences in 2006. In the next few years, he presented posters at a number of conferences including a presentation to the International Society for the Research of Aggression in Budapest, Hungary in 2008.

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