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**Behavioral and Learning Comparisons Between Fast and Slow
Kindling Rat Strains: A Focus on Fear**

Paul Mohapel

1993

**Presented to the Department of Psychology at Carleton
University in partial fulfilment of the requirements for the
degree of Master of Science in Psychology**

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Behavioral and Learning Comparisons Between Fast and Slow
Kindling Rat Strains: A Focus on Fear

submitted by Paul Mohapel, B.Sc.

in partial fulfilment of the requirements for the degree of
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A handwritten signature in black ink, appearing to read "San C. McIvor", written over a dotted line.

Thesis Supervisor, Dept. of Psychology

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Chair, Dept. of Psychology

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Ottawa, Canada

September 1993

Abstract

Two rat strains, selectively bred for their susceptibility to amygdala kindling stimulation, were compared on various electrophysiological, behavioral and learning tasks. These epilepsy-resistant (SLOW kindling) and epilepsy-prone (FAST kindling) strains differed on many electrophysiological properties, including amygdala excitability. Since the amygdala is also implicated in emotional behaviors, the following set of experiments examined strain differences in an assortment of behavioral and learning tasks known to have an emotional component. There were significant strain differences in measurements of exploration, involving novel and familiar environments, as well as in emotional reactivity and fear-based learning. The SLOW strain were more likely to approach a novel object, showed less activity over days in the open-field, a lower ratio of open to total arms entries in the elevated-plus maze, less reactivity to hand capture, more behavioral suppression in the open-field if previously shocked with electricity, greater freezing in the inhibitory avoidance task and slower acquisition in the one-way avoidance task than the FAST rats. All these experiments suggest that the SLOW rats are more expressively fearful than the FAST rats. Further, these observations might imply that relatively suppressed excitability of the amygdala in the SLOW rats mediates their relatively greater expression of fear as compared to the FAST rats.

Acknowledgements

I would like to thank Dan McIntyre who not only provided me with the technical guidance and "cabinet making" skills needed to produce this thesis, but also for his infectious and intoxicating exuberance that he brings to his work.

I also extend my gratitude to Mary Ellen Kelly for providing me with her time, invaluable expertise and training. I will always remember our stimulating debates.

Finally, I thank Laura for her supportive role as my mental and emotional beacon, which has allowed me to successfully navigate and complete this degree.

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Introduction

Once considered as acts of gods, demons or evil spirits, epilepsy has always been among the most common chronic neurological disorders. Historically, the term is derived from the Ancient Greeks to explain 'forces from without that seize a man' (Temkin, 1971). Modern understanding of epilepsy has changed considerably from the past, due to the technological advances made in diagnosis and treatment of this disorder, yet it still is not understood adequately (Masland, 1974; Luders & Lesser, 1987).

The term 'epileptic' describes those individuals who exhibit recurrent seizures, regardless of the causal factors, that are the result of an underlying brain disorder. Seizures can arise from a variety of conditions such as infectious disease, head injury, poisoning, extreme fever, alcohol or drug withdrawal, and metabolic imbalances (Ehrman & Parsons, 1981). Approximately 0.5 to 3% of the world's population are diagnosed with epileptic symptoms (Prince, 1978), while almost 9 percent will have at least one seizure during their lifetime (Hauser & Kurland, 1975).

Among the focal epileptic seizure disorders, those evolved from the temporal lobe are the most common (Penfield, 1954; Engel, 1989). Temporal lobe epilepsy (TLE), or complex partial seizures, is defined by episodic

sequences of altered perception and behavior which are initiated by abnormal recurrent discharging of cells deep in the limbic system (Dreifuss, 1975). During temporal lobe seizure discharge, patients commonly experience activation of viscerosensory or autonomic mechanisms, various types of perceptual phenomena such as auditory and visual hallucinations, and affective changes such as fear and depression (Williams, 1956; Daly, 1975; Gloor et al., 1982; Taylor & Lochery, 1987; Gloor, 1992). The discharges during TLE are normally detected in mesial structures of the temporal lobe which include the amygdala and hippocampus. Many studies have implicated these limbic regions in the pathogenesis of TLE seizures (Penfield, 1954; Margerison & Corsellis, 1966; Engel, 1989; Gloor, 1992).

The amygdala is considered a crucial structure in the pathogenetic mechanisms of temporal lobe seizures. Two important aspects of the role of the amygdala point to this fact: Firstly, the most conventional pathology in human TLE, partial neuronal loss and gliosis, are commonly found in the pathological amygdala; secondly, the amygdala has been shown to contribute to the clinical symptomatology of temporal lobe seizures (Gloor, 1992).

Temporal Lobe Epilepsy and Emotion

Recent evidence suggests that emotional/mood changes represent the most important mental disorder related to

epilepsy (Blumer, 1991), with between 25% and 35% of epileptics experiencing some form of serious psychological problem (Reynolds, 1981). However, today there is considerable controversy about the issue of whether an 'epileptic personality' exists (Hermann & Whitman, 1984; Adamec, 1989). It is evident that patients with TLE manifest characteristic emotional changes, and some investigators have attempted to construct an inventory of these specific traits (Bear & Fedio, 1977; Digman & Inouye, 1986). There is no current consensus on the validity of these behavioral scales (Strauss, 1988; Adamec, 1989).

Among the affective changes, fear/anxiety is considered the most common by-product of human temporal lobe epileptic discharge (Penfield & Jasper, 1954; Daly, 1975; Gloor et al., 1982; Hermann & Whitman, 1984; Spiers et al., 1985; Taylor & Lochery, 1987; Gloor, 1990, 1992; Blumer, 1991). Ictal fear usually can be associated with mild anxiety (such as an increase in epigastric sensation, palpitation and pallor) or range to profound terror (fearful hallucinations or memory flashbacks) (Penfield & Jasper, 1954; Gloor, 1992). This fear response can also be duplicated in many patients by amygdala stimulation (Penfield & Jasper, 1954; Halgren et al., 1978; Gloor et al., 1982).

Before further addressing the topic of epilepsy and related animal models, the next section will first examine the relationship between the amygdala and emotional systems.

The Amygdala and Emotion

Early theories of emotion processes emphasized the important roles of the hypothalamus, cerebral cortex, the anterior thalamus, cingulate cortex, and the hippocampus; while virtually ignoring the significance or existence of the amygdala (Cannon, 1931; Maclean, 1949; LeDoux, 1992). Today, the amygdala is now considered to be the principle structure in the brain's emotional system, while the hippocampus and other limbic structures are thought to be involved in cognitive rather than emotional processes (Halgren, 1992; LeDoux, 1992; Aggleton, 1993).

The prominence of the amygdala's role in emotional systems was first acknowledged with the discovery of the Klüver-Bucy syndrome (Klüver & Bucy, 1937), which refers to the collection of behavioral changes produced by lesions or damage to the amygdala (Weiskrantz, 1956). It was first discovered when temporal lobe lesions in primates produced tameness and docile behavior (Klüver & Bucy, 1937), and the syndrome has even been documented in amygdala lesioned patients (Terzian & Ore, 1955). Generally, studies of the Klüver-Bucy syndrome have stressed the importance of the amygdala in emotional processing, and has demonstrated that sensory stimuli passing through the amygdala are bestowed with emotional and motivational meaning (Weiskrantz, 1956; Horel et al., 1975; Aggleton & Mishkin, 1986; LeDoux, 1992). Thus, when the amygdala is damaged it no longer can code the

sensory stimulus with any emotional significance.

Electrical stimulation of the amygdala produces a complex variety of behavioral and autonomic alterations that are highly indicative of a state of fear (see Davis, 1992). For instance, amygdala stimulation has caused: change in heart rate and blood pressure (eg. Kapp et al., 1982; Harper et al., 1984; Iwata et al., 1987; Davis, 1992), an increase in gastric ulceration (Innes & Tansy, 1980), and altered respiration (Harper et al., 1984). Amygdala lesions extinguish fear conditioned responses in a variety of test situations, such as, conditioned freezing in response to foot shock (Blanchard & Blanchard, 1972) or in a continuous passive avoidance test (Slotnick, 1973).

It is well established that the amygdala plays a crucial role in formation and expression of conditioned fear responses (see LeDoux, 1992). Conditioned fear is defined as the array of behavioral responses that are generated when an initial non-emotional stimulus can acquire the capacity to evoke powerful emotional reaction following a consistent pairing with an aversive stimulus. Typically, conditioned fear responses include freezing, heart rate and arterial pressure elevations (McAllister & McAllister, 1971; Blanchard & Blanchard, 1972; Bouton & Bolles, 1980).

Epilepsy and Genetic Seizure Models

There is a considerable amount of evidence that

suggests that genetic factors are implicated in epilepsy and seizure development in humans and other organisms. In humans, twin studies have shown that the overall correlation rate for epilepsy is 60% for monozygotic twins and 13% for dizygotic twins (Tsuboi & Okada, 1985). Siblings or offspring of epileptics are twice as likely to develop seizures than those in the general population (Ehrman & Parsons, 1981). There has also been considerable evidence that an array of different genetic factors are involved in causing or influencing seizures (Anderson & Hauser, 1988). This genetic heterogeneity in seizure mechanisms further complicates the understanding of human epilepsy.

Genetic animal models of human epilepsy are vital in providing the link between the influence of genetic factors on seizure susceptibility. Various species, including mice, gerbils, rats, baboons, dogs and chickens have been utilized as genetic models of seizure-proneness (Jobe & Laird, 1981). These models allow the analysis of the degree to which genetic variability can account for neurochemical, physiological, or anatomical abnormalities associated with seizure propensity.

Different sensory stimuli are typically employed to induce convulsions in seizure-prone animal strains. For example, the Genetically Epilepsy-prone Rat (GEPR) strains are seizure sensitive to intense acoustic stimuli. The consistent and reproducible seizure profiles of the GEPR

lines makes them a reliable model for examining the properties and effects of an assortment of antiepileptic drugs (Daily et al., 1989). Recently, Holmes et al. (1990) investigated whether frequent seizures could cause learning and behavioral deficits in immature GEPRs. Utilizing such learning and behavioral tests as the T-maze, water-maze, and open-field activity, it was concluded that even brief seizure exposure in these immature GEPRs could cause significant detriments in learning, memory and activity behavior (Holmes et al., 1990).

Amygdala Kindling As A Model Of Epilepsy

Over the past few years, kindling has become one of the most eminent experimental animal models of epilepsy. Kindling refers to the eventual development of seizure activity resulting from repeated administration of electrical stimulation or pharmacological agents to discrete brain areas. Kindling is an extremely robust phenomenon that occurs reliably in most species. Due to its reliability and the ease with which measures of seizure development can be traced, kindling has become a very appealing model for the study of the epileptogenic processes (Racine, 1978).

In electrical kindling, the stimulation initially produces little behavioral effect, but with repetition comes to evoke more behavioral pattern and finally fully

generalized seizures (Goddard et al., 1969). Commonly, the standard method of electrical kindling involves the application of a brief train (1 or 2 sec) of electrical pulses at 60 Hz once daily through a permanently implanted wire electrode. In kindling, at least two important plastic phenomena occur progressively over kindling trials: the first is the reduction in afterdischarge (AD) threshold current, whereby the stimulation will gradually lower the AD threshold on succeeding sessions; the second phenomena deals with the gradual growth and propagation of AD throughout most of the brain, with resulting behavioral manifestations (Racine, 1972a,b). These convulsive behaviors consist of a 5-stage ordered sequence involving: automatism of the facial musculature, head-nodding, forelimb clonus, rearing, and loss of postural control (Racine, 1972b). The effects of kindling are essentially permanent, transynaptic and widespread without any obvious tissue damage (Goddard et al., 1969; Racine, 1978). Moreover, the kindling model distinctively exhibits the epilepsy hallmark features of interictal spikes and spontaneous seizures (Pinel et al., 1975).

Kindling can be induced from a variety of limbic areas extending from the anteriorly located olfactory bulbs to the posterior entorhinal cortex (Goddard et al., 1969). To date, the amygdala remains the most frequently studied kindled structure due to its high susceptibility to evoked

electrographic and behavioral responses. Amygdala kindling has been studied in an assortment of mammalian species and strains (see Cain, 1992). It is important to recognize that the rate of kindling within strains is moderately consistent, for example the Long-Evans Hooded rat requires no less than 8 but no more than 16 AD stimulations to evoke a generalized convulsion from the basal amygdala (Racine, 1972b; Cain, 1992). The collective species and strain evidence suggests that predisposition to seizures may be genetically determined (Cain, 1992).

Kindling-like phenomena has also been reported in humans. Evidence includes patients that have received repetitive electrical stimulation through depth electrodes located in the thalamus in order to diminish perceived limb pain. These patients have since developed partial and subsequent generalized tonic seizures which can be attributed to the "kindling" stimulation from the depth electrodes (Sramka et al., 1977). Further evidence arises from individuals with brain tumors restricted to one temporal lobe. These patients exhibit seizures from each autonomous temporal lobe due to the recurring neuronal bombardment from the damaged lobe to the normal lobe, thus creating a kindling effect in the normal temporal lobe (Morrell, 1979; McNamara et al., 1985).

Behavioral Correlates of Amygdala Kindling

It has been validated that amygdala kindling can lead to changes in a variety of nonepileptic behaviors between seizures, such as learning and memory, sleep, spontaneous motor behavior, fear (Belluzzi & Grossman, 1969; McIntyre & Reichert, 1971; McIntyre & Molino, 1972; Boast & McIntyre, 1977; McIntyre, 1979; Stone & Gold, 1988; Cain, 1992; Nieminen et al., 1992) and predation and defensiveness (Adamec, 1976; Adamec, 1989).

For example, McIntyre and Molino (1972) demonstrated that unilateral amygdala lesioned rats that were kindled in the contralateral amygdala showed similar passive (inhibitory) avoidance deficits as did animals with bilateral lesions. Subsequently, this effect was also shown in bilaterally kindled animals (Boast & McIntyre, 1977). The effects of unilateral amygdala kindling on passive avoidance conditioning is unclear. Some researchers have shown deficits in passive avoidance conditioning (Stone & Gold, 1988), whereas others have reported no disruption in conditioning with unilateral kindling (Boast & McIntyre, 1977; Bawden & Racine, 1979; Peele & Gilbert, 1992). Additionally, it has been shown that unilateral kindling does not impede two-way shuttle box performance (Becker et al., 1992).

Recently, Nieminen et al. (1992) investigated the effects of unilateral amygdala kindling on various

behavioral tests, such as the open-field, elevated-plus maze and elevated bridges. They reported that amygdala kindling decreased exploratory and motor activity in the open-field, decreased boldness on the elevated bridge task, and had anxiogenic effects on the elevated-plus maze. They concluded, in contradiction to the passive avoidance experiments, that amygdala kindling *increases* the normal fear response of rats via the amygdaloid pathways.

It has been established that behavioral correlates of kindling have important species and strain differences. For instance, Tryon maze-bright and maze-dull rats were subjected to kindling stimulation and it was discovered that maze-brights had lower AD threshold in the amygdala but required a greater number of stimulations to manifest generalized convulsions (Zaide, 1974). Leech and McIntyre (1976) amygdala kindled two mouse strains that differed in their ability to learn a passive avoidance task. The DBA/2 strain, which kindled in fewer stimulations, learned the task better with distributed trials; while the C3H/He strain, which required more kindling stimulations, acquired the task better with massed trials. Adamec, whose work on predation and defensiveness in cats, showed that partial kindling (instead of full generalized convulsions) was effective in leading to permanent behavioral changes. These changes include alterations in predatory, intraspecific aggression (Adamec, 1976), or passive avoidance performance

(McIntyre, 1978; Bawden & Racine, 1979). However, partial amygdala kindling in the hooded rat does not effect these behaviors.

Another approach to the study of behavioral associations of amygdala kindling is to examine the correlational studies of pre-kindling behavioral measures and subsequent kindling measures. For instance, Ossenkopp and Sanberg (1979) discovered that rats which urinated more in the open-field, upon subsequent amygdala kindling, exhibited prolonged latencies to clonus onset.

Several investigators have speculated the possible implications of amygdala kindling in clinical behavior disorders, such as dyscontrol, schizophrenia, depression and anxiety (Girgis & Kiloh, 1980; Post, 1983; Stark-Adamec & Adamec, 1986). It has been theorized that a 'kindling-type' of phenomenon may occur in the epileptic human brain, whereby gradual and progressive epileptogenesis could cause brain alterations that lead to eventual expression of interictal behavior abnormalities (Post & Kopanda, 1976; Post, 1983; Stark-Adamec & Adamec, 1986). For instance, it has been suggested that changes in predation and defensiveness in cats due to partial kindling of the amygdala or hippocampus can be interpreted as changes in emotional bias or personality (Adamec, 1976; Adamec, 1989; Adamec, 1990). Specifically, Adamec (1990) argues that increases in defensive behavior of felines, caused by

partial limbic kindling, models certain aspects of anxiety and depression symptoms affiliated with human limbic epilepsy.

FAST and SLOW Amygdala Kindling Rat Strains

In the late seventies, Racine and Steingart succeeded in selectively breeding kindling-prone (FAST kindling) and kindling-resistant (SLOW kindling) rat strains. Originally, the two rat strains were out bred from two parent populations, Wistar and Long Evans Hooded, on the basis of the number of amygdala stimulation trials required to develop the first generalized convulsion. To date various behavioral, electrophysiological and neurochemical differences between these selectively bred animals has been chronicled (Steingart, 1983; Dufresne, 1990; Lennox, 1991).

Steingart (1983) reported that the FAST kindling strain required on average 11.0 trials of stimulation, while the SLOW kindling strains averaged 42.1 stimulations to the first stage-5 generalized convulsion. Recently, Dufresne (1990) replicated Steingart's kindling experiments and found slightly faster amygdala kindling rates for the FAST strain (8.8) and the SLOW strain (31.2). Both Steingart and Dufresne observed no inter-strain differences in afterdischarge (AD) threshold before kindling; however, Dufresne found that the FAST rats had a longer AD duration during the threshold determination. The behavioral

responses associated with these generalized convulsions were also discovered to be different for the two strains; whereby the FAST strain showed partial seizures which occurred in a few trials before generalized seizures, while the SLOW strain exhibited retarded and prolonged partial seizures before generalization development (Steingart, 1983; Dufresne, 1990).

Steingart (1983) further investigated FAST and SLOW strain differences, early in the selection process, with respect to several behavioral tasks including open-field behavior, muricide, hot plate pain sensitivity and passive avoidance behavior. Steingart concluded that the first few generations of the FAST strains were generally more reactive than the SLOW strains.

Purpose

It is well documented that kindling produces epileptic modifications in behavior. Additionally, kindling has also demonstrated changes in non-epileptic behaviors. Extending this observation to the FAST and SLOW kindling rats, the next obvious question is whether selected differences in kindling predisposition are associated with differences in non-epileptic behaviors. Several genotypes may collectively establish a predisposition 'for' or 'against' kindled seizures. If so, then it is reasonable that other phenotypic traits may also be co-expressed by the same

polygenes that determine kindling vulnerability.

In the following experiments we arguably studied temporal lobe excitability without the direct electrical triggering of seizure activity. Knowing that local amygdala excitability is so dramatically different between the FAST and SLOW strains (Dufresne, 1990), and that the amygdala is implicated in emotionally mediated behaviors, we expect to observe significant strain differences in an assortment of behavioral and learning tasks known to have an emotional component.

General Method

BREEDING PROCEDURES:

FAST and SLOW groups of rats were nonselectively bred from the 21st, 22nd and 23rd generations (F21, F22 & F23). The two strains of rats were bred in separate colony rooms. For breeding purposes, a male rat was housed with one or two female rats in a plastic breeding cage (34 x 29 x 17 cm) in a manner which precluded first cousin or brother-sister pairings. The date of birth was recorded for each litter. One month following birth, pups were weaned and housed together in separate plastic cages with siblings of the same gender. Each individual strain animal was identified with labels indicating parentage, breeding cage number and birth date. Approximately two months after birth, all animals

from each strain were transferred into separate holding rooms which contained other non-FAST/SLOW strain rats. When the strain rats were selected for each individual experiment, no more than 2 rats came from the same litter.

SUBJECTS:

All the following experiments were conducted using only male FAST and SLOW strain rats. For each experiment animals were about 90 to 100 days of age, weighing 200 to 350 grams, during testing. Food and water was provided freely at all times throughout the experiments.

Experiment 1

The following behavioral investigations simply compared the strains on naturally occurring, species-specific behavioral responses to novel environments. To do so, the subjects were placed in unfamiliar situations and were compared on either: the change in frequency of occurrence of particular types of behavior over successive exposures to the novel environment, or a set of behaviors during a single novel test exposure. These novel environment tests principally allowed exploratory and/or emotional behaviors to be assessed.

In this experiment we also re-established electro-physiological kindling data on the strains.

A. NOVEL ANIMATE/INANIMATE EXPLORATORY TESTS:

Strain differences in neophilia for the SLOW and FAST rats were evaluated in this experiment. Specifically, this task examined exploratory behavior and response inhibition to novel objects. This test is frequently employed to study genetic variation in response to novel objects (Harrington, 1979a).

Methods

The two strains (20 SLOW & 6 FAST; note that very few FAST rats were available for this experiment due to initially low breeding stocks) were compared on their latency to approach a novel inanimate object and a novel animate object (human hand) placed in their home plastic cage. The experimenter, who had minimal previous contact with the animal, opened the cage lid (about 10 cm) and waited for the rat to settle. The tester then placed his clenched fist into the bin (about 5 cm) and timed the latency for the rat to approach and sniff the hand. Then a vertical panel with a 38 mm hole in the centre was placed into the bin parallel to the front of the cage. The animal was measured on the time it took to poke it's head through the hole to the point where both eyes were beyond the panel surface. The order of presentation, of either the hand or panel first, was randomly counter balanced.

Results and Discussion

Over both novel exploratory tests, the SLOW strain

exhibited shorter mean latencies to approach either the hand or the wooden object in contrast to the FAST strain (Figure 1). However, the novel hand latency differences were significant [$F(1,24)=4.16$, $p=0.05$] while the novel wooden panel differences were not [$F(1,24)=1.07$, $P=0.3$].

In this particular brief acute novelty test paradigm it appeared that the SLOWs showed less inhibited exploratory behavior than the FASTs.

B. KINDLING REDETERMINATION:

The objective of this experiment was to replicate the electrophysiological data for the FAST and SLOW strains reported by Steingart (1983) and Dufresne (1990). Dufresne had described slightly faster kindling rates for both the kindling strains; therefore it important to verify whether the FAST/SLOW strains have deviated in their kindling profiles over the successive generations since 1990. Note that a normal rat requires, on average, 15 stimulations to fully kindle from the amygdala (Goddard et al., 1969). Importantly, just as the kindling rate gives an indication of speed of epileptic recruitment, the initial after-discharge (AD) threshold durations reflect the local excitability of the amygdalae. Dufresne (1990) reported strain differences in the initial AD durations, while Steingart (1983) found no distinctions in this measure.

Figure 1. Mean ($\pm$ S.E.M.) latency of approach to novel objects: either a hand or a wooden panel of SLOW and FAST strains.

Methods

Surgical Procedures. The 20 SLOW and 6 FAST kindling rats, utilized in the previous exploratory experiment, were selected for this experiment. At 120 days of age, the rats were surgically implanted with electrodes. Subjects were anaesthetized with sodium pentobarbital (Somnotol; 60 mg/kg, i.p.) and implanted with four bipolar stimulating/recording nichrome wire electrodes in the bilateral amygdalae (0.2 mm posterior to bregma, 4.5 mm lateral to the midline, 8.2 to 8.5 mm ventral below skull surface) and bilateral hippocampi (3.0 mm posterior to bregma, 3.7 mm lateral to the midline, 3.0 mm ventral). Standard surgical procedures and equipment were employed as reported in Molino and McIntyre (1972). After the surgery, animals were given a two week recovery period before electrophysiological recording and stimulation procedures.

Kindling Procedure and Analyses. The AD thresholds of both amygdalae and both hippocampi were assessed by delivering a 2 second 60 Hz sine wave pulse to each site, starting at 15 μ A and increasing by increments to 25, 35, 50, 75, 100, 200, 250, 300, 350 and 400 μ A every minute until an electrographic AD was recorded. Threshold determination for each site was separated by a 24 hour interval. Each animal had one amygdala randomly selected as the kindling stimulation site. This site was then kindled once daily until a total of six generalized convulsions were evoked

(Racine, 1972).

The strains were compared with respect to their initial AD threshold and durations. The number of trials/ stimulations required to the first generalized stage-5 seizure (i.e. kindling rate) was determined. Once the animals exhibited these generalized seizure profiles, further assessment was made of the latency to onset of forelimb clonus, duration of clonus, and duration of the entire associated AD.

The animals, upon completion of the experiment, were anaesthetized and intracardially perfused with saline rinse followed by 10% formalin. Within 24 hours the brains were removed and stored in 10% formalin until sectioned. The tissue was frozen and sliced at 40 μ m, mounted and stained with Nissl in order to confirm electrode placements.

Results and Discussion

Histology. Sixteen of the original 26 animals had accurate amygdala site placements (12 SLOW, 4 FAST). The majority of these placements were in the medial amygdaloid complex (see Figure 2). The remaining 10 animals were omitted from the electrophysiological analyses.

Amygdala AD Thresholds. No differences were observed in AD thresholds between the strains both before and after amygdala kindling [$F(1,14)=0.97$, $p=0.3$]. Significant differences between the SLOW/FAST strains were apparent in the initial AD duration, evoked during the first AD

threshold determination. The mean AD durations were 8.8 ± 1.3 seconds and 22.0 ± 9.8 seconds for the SLOW and FAST animals, respectively [$F(1,14)=5.4$, $p=0.04$].

Amygdala Site Kindling. The SLOWs required a mean of 58.9 ± 11.0 stimulations to fully develop a generalized stage-5 seizure, while the FASTs had a generalized kindling rate of 15 ± 3.8 stimulations [$F(1,14)=5.02$, $p=0.04$]. The actual motor seizure response profiles were considerably different between the two rat strains. Over the six generalized stage-5 seizures, mean latencies to onset of forelimb clonus were significantly shorter in the SLOWs as compared to the FASTs [$F(1,14)=5.61$, $p=0.03$; Figure 3]. Overall, latencies progressively decreased over successive seizure trials in both strains [$F(5,13)=2.86$, $p=0.02$]. Figure 4 illustrates the significant shorter mean clonus seizure duration of the SLOWs as compared to the FASTs during the six convulsions [$F(1,14)=6.18$, $p=0.03$]; as well seizure durations for both strains increased over successive trials [$F(5,13)=8.2$, $p=0.0001$]. Similarly, there was a significant difference in the mean total AD duration over six stage-5 convulsions, where the SLOWs had a shorter AD [$F(1,14)=44.8$, $p=0.0001$; Figure 5]. However, there was no significant increase in AD duration within the strains over the six convulsive trials [$F(5,13)=1.83$, $p=0.1$]. The initial AD test confirmed differences in local amygdala excitability between the two strains, even though the current intensity required to

Figure 2. A schematic representation of stimulating electrode placements for the SLOW and FAST animals. Dark circles represent electrode placements for the SLOWs, while dark squares represent placements for the FASTs. The three sections represent planes from Bregma: -3.14 mm, -3.60 mm, and -3.80 mm; respectively.

Figure 3. Mean ($\pm$ S.E.M.) latencies to forelimb motor clonus for the six stage-5 seizure trials at the stimulated site. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

Figure 4. Mean ($\pm$ S.E.M.) durations of forelimb motor clonus for the six stage-5 seizure trials at the stimulated site. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

Figure 5. Mean ($\pm$ S.E.M.) total AD durations for the six stage-5 seizure trials at the stimulated site. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

elicit the AD was the same for both strains. The SLOW kindling strain exhibited significantly shorter AD durations, which suggests that the SLOW's amygdala is locally less excitable or more suppressed/inhibited than the FAST's. These findings replicate Dufresne (1990).

The development of generalized seizures was much more prolonged in the SLOW strain compared to the FAST strain. The number of stimulation trials required for the first generalized convulsion were somewhat slower, for both strains, than those reported by Steingart (1983) and Dufresne (1990). This may be due to the fact that the majority of the electrode placements were situated in the medial amygdala nucleus, which is known to have slower kindling rates in normal animals (McIntyre et al., 1992). The FAST animals displayed longer: (a) latencies to forelimb motor seizure clonus, (b) duration of motor seizure clonus, and (c) duration of the total evoked AD. These findings are similar to that of Dufresne (1990) and are probably due to the FAST's ability to recruit more neural populations and/or pathways necessary to support the triggering of a generalized seizure. On the other hand the SLOW's with their briefer AD durations, are curtailed in their ability to recruit the essential cell populations and projection pathways necessary for the triggering of generalized seizures (Dufresne, 1990).

C. ELEVATED-PLUS MAZE:

In the elevated-plus paradigm, the two open and two closed arms generate a conflict by simultaneously activating two naturally opposing tendencies - exploring a new environment versus avoiding open spaces. This creates an anxiogenic component to this test, whereby the animal's response depends on it's natural species-specific genetic response (Pellow et al., 1985; Falter et al., 1992).

Methods

Ten new male rats from each strain, with no prior testing exposure, were employed for the elevated-plus maze experiment. The apparatus was constructed of white plexi-glass and consisted of two open arms (45 X 14 cm), and two enclosed arms (45 X 14 X 40 cm) with an open-roof. The maze was designed such that the two open arms and the two closed arms were situated across from each other, while the entire apparatus was elevated to a height of 50 cm. Alcohol (70%) was used to clean the maze after each animal.

At the beginning of each trial, subjects were placed in the intersection "neutral" area (where the open and closed arms connect). With a 5 minute exposure to the maze, the latency to leave the centre neutral zone and the number of open/total arm entries were evaluated (all 4 paws onto an arm was scored as a full entry, while only 2 paws was scored as half an entry). At the end of the session, all complete and half arm entries were summed.

Results and Discussion

Firstly, although the SLOWS latency (11.5 ± 2.7 sec) to leave the centre of the maze was faster than the FASTs (26.2 ± 8.7 sec), the difference was not significant [$F(1,18)=2.6$, $p=0.1$]. Secondly, the total mean number of arm entries made by the SLOW animals (11.2 ± 1.9) were significantly lower than the FAST animals (21.1 ± 2.9) [$F(1,18)=8.17$, $p=0.01$]. Thirdly, the SLOWS had a lower ratio of open to total arm entries than the FASTs (0.559 ± 0.03 and 0.309 ± 0.05 , respectively) [$F(1,18)=11.3$, $p=0.004$].

In this experiment, the FAST animals clearly exhibited more activity, in terms of higher ambulation, and were less inhibited by the aversive anxiogenic nature of the open arms. In addition the SLOWS shunned the open arms, expressing a stronger avoidance response which could be interpreted as an elevated fear state (Jones, 1987), as compared to the FASTs.

D. EXPLORATION TEST & OPEN-FIELD:

Prior to the first open-field trial, the strain animals were compared on their initiation to explore a *familiar* environment. This task has been used to study genetic variability of initial responses to explore in other rat strains (Harrington, 1971).

Following this brief test, we exposed the rats to the open-field. The use of the open-field test to study

'emotionality' originated with Hall (1934). Since then it has become a standard procedure for the assessment of emotionality, due to its effortless measurement of clearly defined behaviors. The expression of behaviors in this task, however, is dependent upon a variety of factors which interact in many ways (see Walsh & Cummins, 1976). The open-field has been used extensively in behavioral genetic research to classify various inherited dispositions in different animal strains (Hall, 1951; Harrington, 1972).

Methods

Twenty new naive rats of each strain were required for these experiments. Half of the animals of each strain were isolated in a quieter environment and had minimal contact with any animal technicians/personnel prior to the first test date, while the remaining subjects were housed in the normal environment of the care facilities. All the subjects in this experiment were housed in pairs. On the first test day of the open-field, prior to the actual placement of the animal in the arena, the strains were compared on their initiation of exploration in a familiar environment. In the primary space where the animals were housed, their cage lid was opened about 10 cm and the time required for the animals to raise their heads to a point where their eyes were above the lip of the shoe-box was recorded (ceiling time of 180 sec). The experimenter stayed out of view of the rat during

the opening of the lid. After the rats had poked their heads over the lip, the cage was immediately closed and transported to the test room where the open-field apparatus was located.

The open-field apparatus was a box constructed of white plexi-glass with 50 cm high side walls and a 100 X 100 cm floor with 25 equal (10 X 10 cm) squares marked-off with thin black lines. A camera was mounted above the apparatus which allowed the observer to view the rat remotely.

Over the next 4 consecutive days, at the same time of day, alternating SLOW and FAST strain pairs were tested individually in the open-field box. Each animal was placed in the centre square at the beginning of every trial and observed over a 5 minute period. The following observations were taken: (1) the latency required for all four paws to leave the initial starting centre square; (2) total number of rears; (3) total locomotion, (the number of squares entered by all 4 paws of the rat during the 5 minute session). After each animal was removed from the arena, the floor was be wiped clean with 70% alcohol to remove excrement and any residual odors.

Results and Discussion

In the primary housing space, the SLOW rats had a significantly longer latency to poke their eyes over the cage rim than the FASTs (means of 150.1 ± 10.3 and 106.8 ± 13.2 seconds, respectively) [$F(1,38)=6.69$, $p=0.01$]. In fact

most of the SLOW rats exhibited freezing behavior up until the ceiling time (180 sec). Therefore, in initiating exploration of the strain's home environment, the SLOWs were slower to pop up their heads when their cage lid was open.

Figure 6 illustrates the first measure taken from the open-field test: the latency for the animal to move out of the starting centre square. Using the one factor ANOVA analysis, only on Day 3 was there a significant latency difference between strains - the SLOWs were quicker to leave the centre square [$F(1,38)=5.87$, $p=0.02$]. The non-parametric Mann-Whitney U test analysis, however, demonstrated a significantly shorter latency for the SLOWs at each individual consecutive day [Day 1: $z=-2.89$, $p<0.02$; Day 2: $z=-2.02$, $p<0.05$; Day 3: $z=-3.50$, $p<0.002$; Day 4: $z=-2.34$, $p<0.02$]. A two-factor repeated measures ANOVA revealed no significant main effects in the latencies between the strains due to the large variation found in the FASTs' score [$F(1,24)=2.58$, $p=0.1$]; while a two-tailed Mann-Whitney U did indicate a significant difference between the two strains [$z=-3.60$, $p<0.002$]. Additionally, both of the strain's latency scores generally increased over successive days [$F(3,38)=4.11$, $p=0.008$].

The mean rate of rearing per day is shown for each strain in Figure 7. On Day 1 the SLOW rats reared more often than the FASTs [$F(1,38)=11.3$, $p=0.002$], although, on Day 2 the SLOWs rearing activity declined to the same level

Figure 6. Mean ($\pm$ S.E.M.) latencies to leave the starting square of the open-field apparatus for the SLOW and FAST strains over 4 consecutive test days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

Figure 7. Mean ($\pm$ S.E.M.) rate of rearing during a 5 minute test session in the open-field apparatus for the SLOW and FAST strains over 4 consecutive test days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

as the FASTs [$F(1,38)=0.53$, $p=0.5$]. On Days 4 and 5 the SLOW animals rearing declined further, to the point where the FASTs had a significantly higher rearing rate over the SLOWS [$F(1,38)=5.44$, $p=0.03$; $F(1,38)=14.8$, $p=0.0005$]. Unlike the SLOWS, the FAST strains maintained a relatively consistent rearing rate after the first test day.

The open-field locomotion/ambulation activity (number of squares traversed) closely followed the rearing patterns observed between the strains (see Figure 8). On Day 1 the SLOWS were significantly more active [$F(1,38)=5.36$, $p=0.03$]; on Day 2 their activity was reduced to the same level as the FASTs [$F(1,38)=0.13$, $p=0.7$]; on Days 3 and 4 a further decrease in the SLOWS locomotion resulted in a significantly lower ambulation score compared to the FAST [$F(1,38)=5.09$, $p=0.03$; $F(1,38)=14.3$, $p=0.0005$]. Coinciding with rearing pattern, the locomotion means of the FAST basically remained constant over the 4 test days.

Generally, ambulation and rearing are regarded as forms of exploratory behaviors in the open-field. Rearing and ambulation patterns were found to be remarkably similar over the four day test period. Not surprisingly, locomotion has commonly been reported to be positively correlated with rearing (Lester, 1968; see Archer, 1973). On the first test day the SLOWS were very explorative, but this behavior quickly subsided over the following days to an almost non-existent activity. It is unclear, however, whether this

Figure 8. Mean ($\pm$ S.E.M.) number of squares traversed during a 5 minute test session in the open-field apparatus for the SLOW and FAST strains over 4 consecutive test days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

sudden drop in activity in the SLOWs was the result of an increased fear state or simply 'boredom' due to chronic exposure to a familiar environment. Other open-field studies have shown that "emotional" animals tend to initially express high activity to novel and noxious stimuli, which declines over time (eg. Welker, 1957). On the other hand, the FASTs level of exploration rarely wavered over the four test days, indicating that this strain habituated very little over successive trials.

Experiment 2

The purpose of these experiments was to investigate the reactivity of the SLOW and FAST strains when provoked by a potentially discomforting or painful stimuli.

A. REACTIVITY TESTS:

In this experiment, animals were rated on their behavioral reactivity as manifested by (a) resistance to capture, and then (b) by a pencil tap on the base of the tail. This latter task is commonly employed to assess aggressive behaviors in rodents (Seggie, 1971; Pinel et al., 1977).

Methods

Twenty new rats of both strains were examined in a hand capturing test, followed by a single pen tail-tap trial. The hand capturing test consisted of rating the rat's

reaction to the experimenter's attempt in seizing the animal. The responses were scored according to the following scale: calm with no resistance (0); shied away from hand, minimal vocalization (1); running/struggling and loud vocalization (2); leaped and vigorously struggled with biting (3). The pen tail-tap test involved quickly hitting the rat at the base of its tail and categorizing its reaction as: no response (0), flinched and twisted (1), flinched and attempted to escape (2), jumps (3), or jumped over 20 cm in the air (4). In order to avoid biased measures, scoring was performed blind.

Results and Discussion

The hand capture test revealed a significant difference between the strains, where the SLOWs had a mean rating of 0.75 ± 0.20 and the FASTs had a mean of 1.40 ± 0.21 [$z = -2.08$, $p < 0.05$, two-tailed U-test]. With the pen tail-tap test, however, no significant mean differences were observed [$z = -0.56$, $p > 0.10$, two-tailed U-test].

Accordingly, in the hand-capture test the SLOW rats were relatively less reactive and aggressive than the FASTs, in spite of the fact that the mean responses for both strains were fairly low. The lack of differences in aggression between the strains on the pen tail-tap test was probably due to the initial low aggressive responses, and habituation from the hand-capture test which was presented first.

B. PAIN THRESHOLDS AND TRANSFER TO THE OPEN FIELD:

Blanchard et al. (1968) have reported that a single 2 second footshock can produce gross alterations in the behavior of a rat. The most pronounced behavior was a 'crouching' or freezing posture. It was further shown that this freezing posture could be elicited and maintained by the cues of the stimulus situation associated with the shock (Blanchard & Blanchard, 1969).

The first purpose of this experiment was to determine reactivity differences between the two strains in their flinch and jump pain threshold to a footshock. The second purpose was to ascertain whether the brief foot shock experience would subsequently alter the behavior of the rat in the open-field task. Presumably, a shock experience could sensitize the more emotional rats to subsequently emit responses in the open-field not normally seen by their strain.

Methods

Seventeen new SLOW and sixteen new FAST rats were employed in this experiment. Approximately half the animals from each strain received footshock prior to the open-field exposure. On Day 1, the shock group were used to determine the amount of electrical shock required to produce first, a flinch response and then a jump response. The subjects were placed in 50 x 25 x 30 cm stainless steel box and a very low scrambled current was delivered to the grid floor. The

electric current was gradually and continuously increased in intensity until a flinch or a minor physical discomfort was observed, whereby the current was momentarily shut-off. Shortly there after, the current was resumed and the intensity increased again until the animal jumped.

These animals were subsequently utilized as the *shock group* in a second open field experiment. On the other hand, the *non-shock* control group was placed in the shock box but no current was applied. Twenty-four hours after the shock or pseudo-shock experience, both groups were tested in the open-field apparatus for 4 consecutive days (same procedure as outlined in the previous open-field experiment 1D).

Results and Discussion

On average, the SLOW rats required 0.29 ± 0.01 mA of scrambled shock to produce an observable flinch response which was significantly higher than the 0.24 ± 0.01 mA required for the FAST rats [$F(1,15)=24.5$, $p=0.0002$]. The SLOWs also exhibited a significantly higher threshold for shock, compared to the FASTs, in generating a jump/pain response (0.43 ± 0.01 mA versus 0.39 ± 0.01 mA, respectively) [$F(1,15)=5.47$, $p=0.03$]. Clearly the SLOWs were less reactive to shock than the FAST rats.

The next day in the open-field test, the latencies to leave the centre square for shocked and non-shocked strain groups over the 4 day test period is presented in Figure 9. Here it was observed that only on the first day was there a

Figure 9. Mean ($\pm$ S.E.M.) latencies to leave the starting square of the open-field apparatus for shocked and non-shocked SLOW/FAST groups over 4 consecutive test days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles; unbroken lines represent non-shocked controls while dashed lines represents shocked strains.

significant difference between the two combined FAST compared to the two SLOW groups [$F(3,29)=3.97$, $p=0.02$]. On Day 2 only the shocked versus non-shocked SLOW animals were different [$F(1,15)=4.91$, $p=0.04$], while on Days 3 and 4 no significant latency differences were seen. Over days there was a significant increase in the starting latency for all 4 groups [$F(3,29)=10.8$, $p=0.0001$].

Figures 10 and 11 display almost identical rearing and ambulation activities in the open-field. Both the shocked and non-shocked SLOW groups were less active overall as compared to the FAST groups across the 4 test days [rearing: $F(3,29)=6.79$, $p=0.001$; locomotion: $F(3,29)=6.10$, $p=0.002$]. On Day 1, the shocked SLOWS had a significantly lower rearing and ambulation score when compared to the non-shocked SLOWS [respectively: $F(1,15)=4.72$, $p=0.05$; $F(1,14)=8.35$, $p=0.01$], but on the next 3 days the non-shocked SLOWS dropped their activity to the same level of the shocked SLOWS [rearing: $F(1,15)=0.8$, $p=0.4$; locomotion: $F(1,15)=1.1$, $p=0.3$]. In general, the non-shocked SLOWS did not have significantly higher scores than the shocked SLOWS over the 4 test days with respect to rearing [$F(1,15)=2.13$, $p=0.1648$], but they were significant for locomotive activity [$F(1,15)=6.48$, $p=0.02$]. The activity of both shocked/non-shocked FAST groups were never found to be significantly different from each other over the 4 day span [rearing: $F(1,14)=0.1$, $p=0.8$; locomotion:

Figure 10. Mean ($\pm$ S.E.M.) rate of rearing for a 5 minute session in the open-field apparatus for shocked and non-shocked SLOW/FAST groups over 4 consecutive test days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles; unbroken lines represent non-shocked controls while dashed lines represents shocked strains.

Figure 11. Mean ($\pm$ S.E.M.) number of squares traversed during a 5 minute session in the open-field apparatus for shocked and non-shocked SLOW/FAST groups over 4 consecutive test days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles; unbroken lines represent non-shocked controls while dashed lines represents shocked strains.

$F(1,14)=0.03$, $p=0.9$]. Rearing scores slightly decreased over time for both FAST groups [$F(1,14)=4.04$, $p=0.01$], but locomotive scores remained constant over the 4 days [$F(1,14)=1.5$, $p=0.2$].

The data appear to indicate that the FAST kindling rats were not significantly influenced by the earlier shock experience. In fact, all the FAST animals essentially maintained consistent starting latencies and levels of exploratory activity throughout the 4 testing days, indicating a lack of habituation over repeated exposures.

In contrast, the SLOW rats were observed to be more profoundly affected by the pre-exposure to shock. The shocked SLOWS initially (Day 1) had longer latencies to leave the starting square and less ambulation than the non-shocked SLOWS. This reduced activity suggests that the shock experience may have increased the SLOW's emotional/fear state for novel situations. Interestingly, on the following 3 test days both shocked and non-shocked SLOW animals displayed similar decreases in activity (as was observed in open-field experiment 1D).

Experiment 3

In the inhibitory avoidance paradigm, animals must simply learn to inhibit their natural tendency to explore a dark compartment, in order to avoid an aversive shock stimulus. Training in this task elicits a set of

physiological responses which have been identified as 'fear'. The one-trial inhibitory avoidance is particularly useful for research on processes which regulate the storage of new information because the responses are quickly learned, the memory is stable for a substantial time after training, and results obtained correlate well with measures found in other tasks (Gold, 1986). This task is among the most popular with respect to studying genetic variations among animals (Harrington, 1979b).

The following experiments compared the FAST and SLOW strains on step-down latencies and percentage of time spent freezing in a inhibitory avoidance apparatus.

A. TRADITIONAL INHIBITORY AVOIDANCE:

Methods

For this experiment, 10 FAST and 10 SLOW rats were randomly selected from the 40 open-field subjects from experiment 1D. The apparatus used in this experiment was a modified shuttle box ("Reflex-16", Columbus Instruments International Corporation). The box was constructed of stainless steel measuring approximately 50 cm long, 25 cm wide, and 30 cm high. The top was made from clear acrylic, while the entire floor consisted of a grid rods (3 mm stainless-steel spaced about 12 mm apart) which were connected to a constant current stimulator and scrambler programmed to deliver a 0.5 mA (DC) shock. The box was

divided into two distinct compartments: one was converted into a dark chamber with black walls and ceiling, while the other chamber had a wooden platform that covered the entire grid floor.

On both the training and test days of the inhibitory avoidance, each animal was placed onto the wooden platform with its head facing away from the dark half of the apparatus. Step-down latencies were recorded as the time required for the animal to leave the wooden platform and place all 4 paws onto the grid floor in the dark chamber. A 300 second ceiling was imposed on all latency scores. During the initial training trial the grid was electrified upon completion of the step-down response. Once the animal escaped back onto the wooden platform, it was immediately removed from the apparatus and returned to its home cage. Subsequently, the animal's retention of the experience (inhibitory response) was tested 1, 2, and 7 days after the training trial. During these testing trials, the percentage of time spent freezing (total cumulative freezing time divided by the latency time to step-off platform) was calculated. The term 'freezing' was defined as the absence of movement and the maintenance of a rigid, 'catatonic-like' posture.

Results and Discussion

The mean time to enter the dark compartment for the two strains on the Training Day, and on Test Day 1, 2 and 7

following the training day are shown in Figure 12. There were no significant strain differences found on any of the 4 days [$F(1,18)=1.91$, $p=0.2$]. Not only were the initial training latencies the same, but both strains indicated test score means at or near the ceiling level. On the other hand, the FASTs and SLOWS did exhibit very significant differences in the percentage of time showing 'freezing' behavior on the wooden platform during the 3 test days (see Figure 13). On average the SLOWS displayed a much higher percentage of time freezing ($59.1 \pm 8.8\%$) as compared to the FASTs ($19.0 \pm 9.7\%$) [$F(1,18)=28.4$, $p=0.0001$].

The results demonstrate that both the FAST and SLOW rats were very capable of remembering to 'avoid shock' by not stepping off the platform on test days. In contrast, the freezing data would suggest that both strains had distinct patterns of avoidance behavior during testing; the SLOWS were immobile and the FASTs were more active while avoiding the grid. Since the SLOWS were clearly exhibiting more freezing behavior, we suggest they may have been expressing a stronger fear response. In this case a weaker association of cues with shock might readily show strain differences in the step-down task.

B. STEP-DOWN LATENCIES AFTER SHOCK/OPEN-FIELD:

To weaken the associative component of the step-down task and gain further evidence about the sensitivity of the

Figure 12. Mean ($\pm$ S.E.M.) latency to step-down onto a grid in an inhibitory avoidance apparatus. Latencies for initial Training day (T); 1, 2 and 7 days following the training day for SLOW and FAST strains. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

Figure 13. Mean ($\pm$ S.E.M.) percent time spent expressing freezing behavior in an inhibitory avoidance apparatus over 1, 2 and 7 days following the training day, for SLOW and FAST strains. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

two strains, the following experiment was conducted.

This investigation continued with the rats from Experiment 2B, recall that these animals were threshold shocked in the inhibitory apparatus (without the wooden platform or black walls) and then brought to a novel environment (open-field) where only the shocked SLOWs showed altered behavior from controls. After the open-field tests, both the shocked and non-shocked rats were returned to the inhibitory apparatus to be tested for step-down latencies and activity - as indicated below.

Methods

The same 17 SLOW and 16 FAST animals, utilized in the shock pain threshold to open-field experiment, were examined subsequently in the inhibitory avoidance apparatus. Approximately 48 hours after the last open-field session (Day 7), both groups were placed in the inhibitory avoidance box on the wooden platform and their latencies (ceiling of 300 sec) to step-down (which none of the rats had experienced before) and percentage of freezing behaviors were measured.

Results and Discussion

Figure 14 illustrates step-down latencies for the shocked and non-shocked SLOW and FAST rats. An overall treatment difference was discovered [$F(3,29)=13.1$, $p=0.0001$], whereby shocked SLOW and FAST groups had significantly longer step-down latencies than

Figure 14. Mean ($\pm$ S.E.M.) latency to step-down onto a grid in an inhibitory avoidance apparatus, after for 4 days of testing in an open-field test, for shocked and non-shocked SLOW and FAST strains. and non-shocked groups.

associated controls [$F(1,15)=15.0$, $p=0.002$; $F(1,14)=10.5$, $p=0.006$; respectively]. An interaction was also evident where the shocked SLOWS had significantly longer latencies than the shocked FASTs [$F(1,15)=9.55$, $p=0.008$]. In addition significant differences were apparent in the percent of freezing time in the inhibitory box between the groups [$F(3,29)=13.2$, $p=0.0001$]. Non-shocked SLOWS and FASTs spent 0% of their time freezing, while the shocked SLOWS froze $54.9 \pm 13.3\%$ of the time [$F(1,15)=15.2$, $p=0.001$] compared to the shocked FAST's mean freezing time of only $7.1 \pm 3.9\%$ [$F(1,14)=3.34$, $p=0.09$]. The squared correlation coefficient between step-down latencies and proportion of freezing behavior in the inhibitory task was determined to be 0.93 ± 0.09 [$F(1,31)=403.2$, $p=0.0001$].

It was evident that both shocked strains were significantly more inhibited in stepping-down from the platform as compared to their respective controls and, more importantly, the SLOWS exhibited significantly more freezing or fear (and/or perhaps a better retention) of the specific cues of the aversive shock experience than the FAST rats. One might conclude that the original shock experience energized an emotional-fearful response which could be elicited by not only specific cues in the training environment, but possibly by non-specific cues in a novel environment (Experiment 2B).

Experiment 4

ONE-WAY ACTIVE AVOIDANCE:

If the SLOW strain is more fearful of aversive stimulation than the FAST strain, we questioned whether fear could be used to energize enhanced motor behavior rather than the suppressed motor behavior seen in the inhibitory avoidance.

A large number of studies of strain differences in avoidance conditioning have been carried out with an assortment of strains (e.g. Broadhurst & Levine, 1963; Harrington, 1979c). Distinct from the inhibitory avoidance, active avoidance learning is thought to occur when fear is classically conditioned to a conditioned stimulus (CS) which is assumed to serve as the motivator and reinforcement for the instrumental avoidance response (Mowrer, 1947). In typical active avoidance learning, a distinct CS is presented at some interval of time prior to shock (US) onset. An instrumental response (i.e., movement away from the shock area) made during the CS-US interval results in an avoidance of shock, while such a response made after the onset of the US produces only an escape response.

Methods

A new group of 20 FAST/SLOW rats were tested in this experiment. The one-way avoidance box apparatus was the same as used for the inhibitory avoidance tests. Now the

box was separated into two compartments by a metal partition with a 9.5 cm semicircular opening which could be closed-off with a sliding wooden guillotine door. Movement from one compartment to the second was sensed by a pair of photo electric beams which acted to automatically shut-off a stop watch, as well as the CS and US. In this experiment, a compound CS was used consisting of a light bulb that illuminated from about 22 lx to 800 lx, a sound set to produce roughly 80 dB of white noise below the speaker, and an opening guillotine door. The floor of the start-compartment was constructed of stainless steel grids, while the safe-compartment contained the wooden platform.

On the first day of the experiment, each subject was handled for 2 minutes. On the following day, 20 one-way avoidance trials were administered. Each trial began by placing the animal in the start-compartment of the box, facing away from the door. Thirty seconds after the subject was placed in this compartment the light, sound and raised door CS was initiated and, after 5 sec, a scrambled foot shock was delivered (0.5 mA). The shock continued until the animal escaped into the safe-chamber or until 60 sec had elapsed. Leaving the shock compartment prior to shock onset was designated as an avoidance response, while those responses following shock onset were escape responses. Once the animal had made its response, it was immediately returned to the start chamber for 30 sec before the next

trial was begun. If an avoidance/escape response did not occur, then the rat was lifted from the start compartment and placed in the safe compartment for 10 sec. Subsequently the rat was returned to the start box for the next trial. The criterion established for learning the task required that the animal made at least 3 successful avoidances from shock in any 5 consecutive trials.

During testing, the overt stress reactions of the animals were rated on a simple scale, where (1) represented almost no vocalization during shock; (2) represented a low whine or squeal only during shock application; and (3) depicted loud vocalizations during the CS and shock with laboured respiratory 'wheezing' noise or hyperventilation.

Animals were returned to the apparatus one week later and retested on their retention of the task with the same learning criterion as outlined for the acquisition test.

Results and Discussion

The mean number of trials required to learn the one-way avoidance task for the Acquisition test and for the Retention test (7 days later) is plotted in Figure 15. The SLOW animal took significantly longer than the FAST rat to acquire the avoidance task on both the Acquisition test day [$F(1,31)=5.55$, $p=0.03$] and the Retention test day [$F(1,30)=9.55$, $p=0.004$].

Also, during the avoidance testing, the SLOW rats had mean overt stress reaction score of 2.3 ± 0.1 , which was

Figure 15. Mean ($\pm$ S.E.M.) number of trials to learn an one-way avoidance task on the Acquisition and Retention (1 week later) days. SLOW strains are represented by open boxes, while the FASTs are represented by closed circles.

significantly higher than the FASTs mean score of 1.4 ± 0.1 ($z=-3.22$, $p<0.002$, two-tailed Mann-Whitney U test).

Since the SLOWS displayed more overt distress, one could again surmise that these strain animals expressed more 'fear' than the FASTs. However, this fear response did not facilitate the performance of the SLOWS in the one-way avoidance task. This could be because freezing responses interfered with avoidance responses (eg. Bintz et al., 1970) or that the SLOWS were less 'bright' than the FASTs. Unfortunately the difference between motivation, learning and performance variables cannot be discriminated in this experiment. From the previous experiments, however, the SLOWS had expressed powerful freezing responses when shocked; a natural disposition for freezing behavior proves useful in the inhibitory avoidance tasks but detrimental in active avoidance responses, where the animal must move away from the shock.

General Discussion

Our electrophysiological assessment of the amygdala verified that the SLOW and FAST strains retained their distinct kindling rates and convulsion profiles since they were last examined by Dufresne (1990). As expected, the triggered excitability of the SLOW's amygdala was found to be much less than the FAST's amygdala.

In the main body of the thesis it was further established that the two strains were different on nearly all behaviors examined. These differences were apparent in measurements of exploration, involving novel and familiar environments, as well as in emotional reactivity and emotional-based learning.

Exploration and Emotionality in Novel and Familiar Environments

Before discussing the behavioral differences between the SLOW and FAST strains in the novel environment tests, the concepts of emotionality and exploration should be addressed. In animal behavioral testing, the construct of emotionality has been used typically as a general descriptive term, and suggests that different behavioral responses are energized by a *single* central emotional mechanism (e.g., Broadhurst, 1957). However, since most measures of emotionality can be greatly influenced by other 'non-emotional variables' such as sex, litter size, biological rhythms, prior test experience (Walsh & Cummins, 1976; Royce, 1977), a more precise definition of emotionality has been proposed. This definition states that emotionality triggered in novel environments has drive-like properties that facilitates or innibits *many* species-specific behaviors (Archer, 1973).

Ambulation and rearing in novel environments has

traditionally been used as a prime measure of exploration (Archer, 1973). Commonly the assumption is made that exploration is inversely related to emotion or fear. The rationale is that emotional states energize responses which compete with exploratory activity and, therefore, cause low activity (Broadhurst, 1958; Denenberg, 1969). However, some researchers argue that exploration signifies *high* emotional states and, because a novel environment stimulates the animal's arousal, activity increases (Halliday, 1967). On the other hand, Lester (1968) suggested a 'U'-shaped relationship whereby high and low emotional states are associated with low exploration while intermediate emotional states produce the highest levels of activity. Historically in novel environment tests, it is important to note that the terms 'fear' and 'emotionality' have been used synonymously (e.g., Hall, 1934; Broadhurst, 1958; Gray, 1971), although fear is usually viewed as a specific type of emotion which can become associated with a specific stimulus.

Are the SLOW and FAST strain rats differentially emotional? In the present experiments, both the elevated-plus maze and the open-field task revealed the SLOW rats to be less active overall than the FAST rats. Recall, in the open-field test, the SLOW strain exhibited very high activity levels only on Day 1 which quickly subsided over the following days. It is difficult to ascertain the reason for the SLOW's sudden drop in activity in the open-field

test. One possible explanation is that the SLOW rats may have acquired fear (i.e. high emotionality) with repeated exposure to the apparatus. The results from the elevated-plus maze suggest the SLOW rats are more fearful than the FAST rats, since this task is known to have a higher anxiogenic component than the open-field (Jones, 1987).

Alternatively, it is equally plausible that the sudden drop in exploration in the open-field by the SLOW rats was due simply to habituation, and the SLOWs were merely expressing relative 'boredom'. For example, when introduced into a new environment for the first time, speculatively, the SLOW rat's natural curiosity transiently may overcome their more usual lower activity, and thus show a relatively large increase in exploration. This, of course, was observed both on Day 1 of the open-field test and in the initial exploration of a novel hand/object test. However, once the SLOW rats become familiar with an environment, behavioral inhibition predominates. This was shown in both the open-field (Day's 2, 3 & 4) and the home cage exploratory head-poke experiment. Therefore, the SLOW rat's lower activity can be more easily attributed to its naturally inhibited or unexcited state, and not necessarily to increased fear. In addition, the initially shorter latencies of the SLOWs to leave the centre in the open-field support a non-fear interpretation, since a more fearful animal would be expected to freeze and show longer

latencies. Furthermore, non-systematic observations of the SLOW's behavior during the low activity periods in the open-field (Days 2 to 4) also suggests that their behavioral inhibition was not necessarily fear-based (like freezing) since these animals were engaged in grooming behaviors. On the other hand, the FAST rats do not appear to suppress their behavior to the same degree as the SLOW rats, which, results in high ambulation with little habituation.

Reactivity and Non-specific Fear In A Novel Environment

In experiments examining reactivity, the SLOW rats were determined to be less reactive to hand capture than the FAST rats. The reduced reaction of the SLOW rats was seen additionally in the shocked threshold experiment. Here, the SLOW rats were less reflexively reactive to footshock by showing higher flinch and jump thresholds compared to the FAST rats. These findings appear to reflect the SLOWs naturally restrained behavior and/or the FASTs relatively greater excitability.

There was an interesting, non-specific effect of electric footshock between the two strains upon subsequent exposure to the open-field. If shocked beforehand, the SLOW rats did not exhibit their previous Day 1 high exploration activity in the open-field test (Experiment 1D). Unlike the open-field test in Experiment 1D, the lack of activity in the SLOWs in Experiment 2B may have been due to an increase

in non-specific fear rather than general 'boredom'. The SLOW rat's natural disposition towards suppressed behavior combined with the earlier shock experience likely energized a fear-motivated behavioral inhibition. Mos et al. (1973) examined the effects of previous shock on mice in open-field measures and also discovered decreased ambulation scores. As with the mice, shocked SLOW rats seemed to experience *non-specific* fear conditioning which transferred to a new environment not associated with the shock stimulus. In contrast, regardless of previous shock, the FAST rats demonstrated high exploratory behavior in the new environment, and were apparently far less fearful (non-specifically) than the SLOWs. The only potential specific fear object common to both the original shock experience and the open-field test was the experimenter.

Learning In Inhibitory and One-Way Avoidance Tasks

In the inhibitory and one-way avoidance experiments, the animals presumably learn relatively *specific* fear cues which are tested in the same environment that they are trained. An important distinction, however, is made between these two avoidance tasks. In the inhibitory avoidance task the rat is exposed to apparatus cues, steps-down from the wooden platform, and is shocked. The shock-triggered fear is associated with the various proximal cues, and later, the rat is tested for retention of the cue-fear association by

manifesting response inhibition. Conversely, in the one-way avoidance task, the rat initially must perform a motorically active response to escape the shock, and, later to anticipate and avoid the shock.

The inhibitory avoidance experiment demonstrated that both strains were very capable of learning the task, however, the SLOW rats exhibited a more suppressed response (stronger freezing) during the retention test. This finding further supports the notion that the SLOWs manifest stronger behavioral suppression in the face of significant fear arousal. We suggest that if the "ceiling time" measurement in the inhibitory avoidance experiment had been extended beyond the allotted 3 minutes, the FAST rats eventually would have stepped down from the platform since, unlike the SLOW rats, many of them had repeatedly placed their front forelimbs onto the grid during the criterion "avoidance" response.

The suspicion that the FAST rats were less capable of showing and/or retaining the inhibitory fear response was clarified in experiment 3B. Recall that after threshold shock and open-field experience in experiment 2B the rats were returned to the shock box, which was converted into the inhibitory avoidance apparatus. The previously unshocked SLOW and FAST rat controls immediately stepped down from the wooden platform, while the shocked SLOW rats demonstrated considerable fear by having significantly longer step-down

latencies compared to all other groups. It is clear that the SLOW rats were better than the FAST rats at suppressing their step-down exploratory behavior, but it was not possible to determine whether this response inhibition was due to an enhanced cue-specific memory or a non-specific, generalized fear to an apparatus similar to the original shock box. The evidence from open-field experiment 2B suggested non-specific fear learning, since the shocked SLOWs still displayed significant behavioral restraint in this completely novel environment. Alternatively, the experimenter could have represented the specific cue for fear which triggered the SLOW's responses in the open-field.

When the strains were further examined in the one-way active avoidance task, the SLOW rats proved to be inferior to the FAST rats in acquiring the active avoidance performance criterion and retaining the response. Once again, as in the inhibitory avoidance task, these results do not indicate clearly whether the two strains differed in their ability to learn the avoidance response, or in their ability to perform the avoidance response.

It is possible that the SLOW's poorer active avoidance acquisition was based on learning differences. For example, on both the active avoidance training and retest days the SLOW and FAST rat's acquisition rate differed by almost a 100%. On the other hand, in a less aversive escape task, the Morris water-maze, the SLOW rats were superior

performers as compared to the FAST rats (Armstrong & McIntyre, 1992). This was also true in two appetitive tasks: the radial arm-maze (Smith, 1993) and the T-maze (McLeod, 1993). Other studies on the genetic determinants of avoidance learning differences in rat strains suggest that the common characteristic that differentiates most strains are based on emotional or performance, rather than learning differences (Brush, 1991).

It could be argued easily that the SLOW's poorer active avoidance acquisition was the result of a performance rather than a learning problem. Recall that the SLOW rats had a higher overt stress score than the FAST rats while being trained and tested. Here, the SLOWs were sometimes observed to alternate between two extreme reactions during exposure to the shock, either (a) freezing, or (b) frantic jumping. Yet, the drive derived from this intense arousal was not easily translated into an appropriate active avoidance response. It appears that the SLOWs express powerful behavioral inhibition when frightened. This, of course, was appropriate and beneficial in the inhibitory avoidance task, but was counter productive in the active avoidance task. As Blanchard and Blanchard (1969) previously showed, freezing behavior must be extinguished before active avoidances can be made. In contrast, the FAST rats did not express nearly the same intensity or duration in freezing behavior as the SLOW rats and, hence, were readily capable of performing the

one-way avoidance response.

Amygdala Excitability and Fear

The final question to be addressed is whether these various emotional behaviors and learning differences between the two strains are associated with differences in local amygdala excitability? Since amygdala kindling stimulation in rats often produces freezing behavior, one might expect that a more excitable amygdala would be associated with a more robust fear response. Additionally, since neural plasticity is related to excitability, one might predict better fear learning to occur in the more excitable amygdala tissue. Thus we expected the SLOWs to be inferior fear learners compared to the FASTs. Yet, with the exception of one-way avoidance learning, the opposite was true. The SLOW rats with their inhibited local amygdala AD were more fearful than the FAST rats. Reduced amygdala activity, therefore, appears to be related positively to fear behaviors. This suggestion is partially supported by the fact that amygdala activation by electrical stimulation equally often produces aggression, not freezing behavior, in humans and other animals (Pinel et al., 1977; see Davis, 1992).

Amygdala excitability variations, as found in the SLOW/FAST strains, have also been documented in other rat strains. Zaide (1974) reported that Tryon Maze-Bright rats

had slower kindling rates and shorter initial AD durations than Tryon Maze-Dull rats. Further, it was determined that AD thresholds and AD durations were closely correlated with the strain differences in behavioral inhibition, where Maze-Bright rats were better at inhibiting their behavior. These data are remarkably similar to our FAST and SLOW strains where the Maze-Brights behave like our SLOW rats, and further implicate the important role of amygdala excitability in behavioral inhibition.

When considering the underlying brain mechanisms of fear, the contribution of the amygdala is undeniable. As discussed previously, electrical stimulation of the amygdala can produce a complex pattern of behavioral and autonomic changes that often contains fear, while lesions of the amygdala can block the effects of fear conditioning in a variety of test situations (see Davis, 1992) and increase exploratory behavior in a open-field test (Jellestad & Cabrera, 1986).

Pharmacological manipulations of neurotransmitter system locally in the amygdala have produced many alterations in emotionality and fear learning. The noradrenergic (Liang et al., 1986) system has been found to facilitate, while the GABAergic (Brioni et al., 1989) and peptidergic (Gallagher & Kapp, 1978; Introini-Collison et al., 1989) systems impede inhibitory avoidance learning. In addition, local infusion of N-methyl-D-aspartate (NMDA)

receptor antagonists into the amygdala have been shown to impair one-trial inhibitory avoidance training (Liang & Davis, 1990), freezing (Fanselow et al., 1991) and fear-potentiated startle (Miserendino et al., 1990; Campeau et al., 1992). Thus many transmitter systems modulate fear in the amygdala.

The amygdala certainly is not the only brain structure involved in emotional expression or fear learning. For example, it has recently been shown that amygdala lesions interfere with fear conditioning to both the specific and non-specific cues of the shock apparatus, while hippocampus lesions interfere only with non-specific cues (Phillips & LeDoux, 1992). In general, the amygdala is thought to provide an associative role in fear conditioning, where it mediates memory for affect information. It has been suggested that other structures, such as the hippocampus mediates memory for spatial and temporal attributes, while the caudate nucleus mediates memory for motor responses and the visual cortex mediates memory for visual sensory-perceptual information (Kesner et al., 1993).

In conclusion the SLOW amygdala kindling rat strain, with their intrinsically more suppressed local amygdala excitability, were shown be naturally as much, or more, inquisitive than the FAST rats with respect to exploratory behavior until aversive qualities were introduced. When the

SLOWs were activated with fear, a relatively robust behavioral suppression was expressed. This fear-motivated inhibitory behavior proved to be advantageous in a inhibitory avoidance task, but detrimental in an active avoidance task. On the other hand the FAST rats, with their greater local amygdala excitability, expressed little behavioral inhibition throughout most of these behavioral and learning tasks.

In order to further elucidate differences in emotionality between the SLOW and FAST strains, future studies should utilize tests that look at purely fear-based behaviors without the contaminating influences of learning and memory. One such paradigm, for example, is the fear-potentiated startle task which allows fear to be triggered by a cue (such as a loud noise) that was never associated with the previous shock experience (McAllister & McAllister, 1971; Davis, 1992).

References

- Adamec, R.E. (1976). Behavioral and epileptic determinants of predatory attack in the cat. In Wada, L. (Ed.), Kindling, New York: Raven Press, pp.73-87.
- Adamec, R.E. (1989). Kindling, anxiety and personality. In Bolwig, T.G. & Trimble, M.R. (Eds.), The Clinical Relevance of Kindling, New York: John Wiley & Sons Ltd, pp.117-135.
- Adamec, R.E. (1990). Kindling, anxiety and limbic epilepsy: Human and animal perspectives. In Wada, J.A. (Ed.), Kindling 4, New York: Raven Press, pp.329-341.
- Aggleton, J.P. (1993). The contribution of the amygdala to normal and abnormal emotional states. Trends In Neuroscience, 16, 328-333.
- Aggleton, J.P. & Mishkin, M. (1986). The amygdala: Sensory gateway to the emotions. In Plutchik, R. & Kellerman, H. (Eds.), Emotion: Theory, Research and Experience, Vol.3, Orlando: Academic Press, pp.281-299.
- Anderson, V.E. & Hauser, W.A. (1988). Genetics. In Laidlaw, J., Richens, A. & Oxley, J. (Eds.), A Textbook of Epilepsy (3rd ed.), New York: Churchill Livingstone, pp.49-77.
- Archer, J. (1973). Tests for emotionality in rats and mice: a review. Animal Behaviour, 21, 205-235.
- Armstrong, J.N. & McIntyre, D.C. (1992). Unpublished observations.
- Bawden, H.N. & Racine, R.J. (1979). Effects of bilateral kindling or bilateral sub-threshold stimulation of the amygdala or septum on muricide, ranacide, intraspecific aggression and passive avoidance in the rat. Physiology and Behavior, 22, 115-123.
- Bear, D.M. & Fedio, P. (1977). Quantitative analysis of interictal behavior in temporal lobe epilepsy. Archives of Neurology, 34, 454-467.
- Becker, A., Grecksch, G., Ruthrich, H.L., Pohle, W., Marx, B., & Matthies, H. (1992). Kindling and its consequences on learning in rats. Behavioral and Neural Biology, 57, 37-43.

- Belluzzi, J.D., & Grossman, S.P. (1969). Avoidance learning: Long-lasting deficits after temporal lobe seizures. Science, 166, 1435-1437.
- Bintz, J. Kellicutt M., & Peacock, K. (1970). Avoidance conditioning and movement-contingent US presentation. Journal of Comparative and Physiological Psychology, 72, 250-256.
- Blanchard, D.C. & Blanchard, R.J. (1972). Innate and conditioned reactions to threat in rats with amygdaloid lesions. Journal of Comparative and Physiological Psychology, 81, 281-290.
- Blanchard, R.J. & Blanchard, D.C. (1969). Crouching as an index of fear. Journal of Comparative and Physiological Psychology, 67, 370-375.
- Blanchard, R.J., Dielman, T.E. & Blanchard, D.C. (1968). Prolonged aftereffects of a single foot shock. Psychonomic Science, 10, 327-328.
- Blumer, D. (1991). Epilepsy and disorders of mood. In Smith, D., Treiman, D. & Trimble, M. (Eds.), Advances in Neurology, Vol.55: Neurobehavioral Problems in Epilepsy, New York: Raven Press, pp.185-195.
- Boast, C. & McIntyre, D.C. (1977). Bilateral kindled amygdala foci and inhibitory behavior in rats: A functional lesion effect. Physiology and Behavior, 18, 25-28.
- Bouton, M.E. & Bolles, R.C. (1980). Conditioned fear assessed by freezing and by the suppression of three different baselines. Animal Learning and Behavior, 8, 429-434.
- Brioni, J.D., Nagahara, A.H. & McGaugh, J.L. (1989). Involvement of the amygdala GABAergic system in the modulation of memory storage. Brain Research, 487, 105-112.
- Broadhurst, P.L. (1957). Emotionality and the Yerkes-Dodson law. Journal of Experimental Psychology, 54, 345-35..
- Broadhurst, P.L. (1958). Determinants of emotionality in the rat. III. Strain differences. Journal of Comparative and Physiological Psychology, 51, 55-59.
- Broadhurst, P.L. & Levine, S. (1963). Behavioral consistency in strains of rats selectively bred for emotional elimination. British Journal of Psychology, 54, 121-

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STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

125.

- Brush, F.R. (1991). Genetic determinants of individual differences in avoidance learning: Behavioral and endocrine characteristics. Experientia, 47, 1039-1050.
- Cain, D.P. (1992). Kindling and the amygdala. In Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, New York: Wiley-Liss, Inc., pp.539-560.
- Campeau, S., Miserendino, M.J.D. & Davis, M. (1992). Intra-amygdala infusion of the N-methyl-D-aspartate receptor antagonist AP5 blocks acquisition but not expression of fear-potentiated startle to an auditory conditioned stimulus. Behavioral Neuroscience, 106, 569-574.
- Cannon, W.B. (1931). Again the James-Lange and the thalamic theories of emotion. Psychological Review, 38, 281-295.
- Daily, J.W., Reigel, C.E., Mishra, P.K., & Jobe, P.C. (1989). Neurobiology of seizure predisposition in the genetically epilepsy-prone rat. Epilepsy Research, 3, 3-17.
- Daly, D.D. (1975). Ictal clinical manifestations. In Penry, J.K. & Daly, D.D. (Eds.), Advances in Neurology, Vol.11: Complex Partial Seizures and Their Treatment, New York: Raven Press, pp.57-83.
- Davis, M. (1992). The role of the amygdala in conditioned fear. In Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotional, Memory, and Mental Dysfunction, New York: Wiley-Liss, Inc., pp.255-305.
- Denenberg, V.H. (1969). Open field behavior in the rat: what does it mean? Annual New York Academy of Science, 159, 852-859.
- Digman, J. & Inouye, J. (1986). Further specification of the five robust factors of personality. Journal of Personality and Social Psychology, 50, 116-123.
- Dreifuss, F.E. (1975). The differential diagnosis of partial seizures with complex symptomatology. In Penry, J.K. & Daly, D.D. (Eds.), Advances in Neurology, Vol.11: Complex Partial Seizures and Their Treatment, New York: Raven Press, pp.187-199.
- Dufresne, C. (1990). Seizure Development in kindling fast and kindling slow rat strains. Unpublished master's

thesis, Carleton University, Ottawa.

Ehrman, L., & Parsons, P.A. (1981). Behavior Genetics and Evolution, New York: McGraw-Hill.

Engel, J. (1989). Seizures and Epilepsy, Philadelphia: FA Davis.

Falter, U., Gower, A.J., & Gobert, J. (1992). Resistance of baseline activity in the elevated plus-maze to exogenous influences. Behavioural Pharmacology, 3, 123-128.

Fanselow, M.S., Kim, J.J. & Landeira-Fernandez, J. (1991). Anatomically selective blockade of Pavlovian fear conditioning by application of an NMDA antagonist to the amygdala and periaqueductal gray. Society for Neuroscience Abstract. 17, 659.

Gallagher, M. & Kapp, B.S. (1978). Manipulation of opiate activity in the amygdala alters memory processes. Life Sciences, 23, 1973-1978.

Girgis, M. & Kiloh, L.G. (Eds.) (1980). Limbic Epilepsy and the Dyscontrol Syndrome, New York: Elsevier.

Gloor, P. (1990). Experiential phenomena of temporal lobe epilepsy: Facts and hypotheses. Brain, 113, 1673-1674.

Gloor, P. (1992). Role of the amygdala in temporal lobe epilepsy. In Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, New York: Wiley-Liss, Inc., pp.505-538.

Gloor, P., Olivier, A., Quesney, L.F., Andermann, F., & Horowitz, S. (1982). The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Annals of Neurology, 12, 129-143.

Goddard, G.V., McIntyre, D.C., Leech, C.K. (1969). A permanent change in brain function resulting from daily electrical stimulation. Experimental Neurology, 25, 295-330.

Gold, P.E. (1986). The use of avoidance training in studies of modulation of memory storage. Behavioral and Neural Biology, 46, 87-98.

Gray, J.A. (1971). The Psychology of Fear and Stress, London: Weidenfeld & Nicolson.

Halgren, E. (1992). Emotional neurophysiology of the

- amygdala within the context of human cognition. In Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotional, Memory, and Mental Dysfunction, New York: Wiley-Liss, Inc., pp.191-228.
- Halgren, E., Walter, R.D., Cherlow, D.G. & Crandall, P.H. (1978). Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. Brain, 101, 83-117.
- Hall, C.S. (1934). Emotional behavior in the rat: I. Defecation and urination as measures of individual differences in emotionality. Journal of Comparative Psychology, 18, 385-403.
- Hall, C.S. (1951). The genetics of behavior. In Stevens, S. (Ed.), Handbook of Experimental Psychology, New York: Wiley, pp.304-330.
- Halliday, M.S. (1967). Exploratory behaviour in elevated mazes. Quarterly Journal of Experimental Psychology, 19, 254-263.
- Harper, R.M., Frysinger, R.C., Trelease, R.B. & Marks, J.D. (1984). State-dependent alteration of respiratory cycle timing by stimulation of the central nucleus of the amygdala. Brain Research, 306, 1-8.
- Harrington, G.M. (1971). Strain differences among rats in initiating exploration of differing environments. Psychonomic Science, 23, 348-349.
- Harrington, G.M. (1972). Strain differences in open-field behavior of the rat. Bulletin of the Psychonomic Society, 27, 51-53.
- Harrington, G.M. (1979a). Strain differences in neophilia in the rat. Bulletin of the Psychonomic Society, 14, 424-426.
- Harrington, G.M. (1979b). Strain differences in passive avoidance conditioning of the rat. Bulletin of the Psychonomic Society, 13, 157-158.
- Harrington, G.M. (1979c). Strain differences in shuttle avoidance conditioning in the rat. Bulletin of the Psychonomic Society, 13, 161-162.
- Hauser, W.A. & Kurland, L.T. (1975). The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia, 16, 1-66.

- Hermann, B.P. & Whitman, S. (1984). Behavioral and personality correlates of epilepsy: A review, methodological critique, and conceptual model. Psychological Bulletin, 95, 451-497.
- Holmes, G.L., Thompson, J.L., Marchi, T.A., Gabriel, P.S., Hogan, M.A., Carl, F.G. & Feldman, D.S. (1990). Effects of seizures on learning, memory, and behavior in the genetically epilepsy-prone rat. Annals of Neurology, 27, 24-32.
- Horel, J.A., Keating, E.G. & Misantone, L.J. (1975). Partial Klüver-Bucy syndrome produced by destroying temporal neocortex or amygdala. Brain Research, 94, 347-359.
- Innes, D.L. & Tansy, M.F. (1980). Gastric mucosal ulceration associated with electrochemical stimulation of the limbic system. Brain Research Bulletin, 5, 33-36.
- Introini-Collison, I.B., Nagahara, A.H. and McGaugh, J.L. (1989). Memory-enhancement with intra-amygdala post-training naloxone is blocked by concurrent administration of propranolol, Brain Research, 476, 94-101.
- Iwata, J., Chida, K. & LeDoux, J.E. (1987). Cardiovascular responses elicited by stimulation of neurons in the central amygdaloid nucleus in awake but not anaesthetized rats resemble conditioned emotional responses. Brain Research, 418, 183-188.
- Jellestad, F.K. & Cabrera, I.G. (1986). Exploration and avoidance learning after ibotenic acid and radio frequency lesions in the rat amygdala. Behavioral and Neural Biology, 46, 196-215.
- Jobe, P.C. & Laird, H.E. (1981). Neurotransmitter abnormalities as determinants of seizure susceptibility and intensity in the genetic models of epilepsy. Biochemical Pharmacology, 30, 3137-3144.
- Jones, R.B. (1987). Fear and fear responses: a hypothetical consideration. Medical Sciences Research, 15, 1287-1290.
- Kapp, B.S., Gallagher, M., Underwood, M.D., McNall, C.L. & Whitehorn, D. (1982). Cardiovascular responses elicited by electrical stimulation of the amygdala central nucleus in the rabbit. Brain Research, 234, 251-262.
- Kesner, R.P., Bolland B.L. & Dakis, M. (1993). Memory for spatial locations, motor responses, and objects: triple

dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex. Experimental Brain Research, 93, 462-470.

Klüver, H. & Bucy, P.C. (1937). "Psychic blindness" and other symptoms following bilateral temporal lobectomy in rhesus monkeys. American Journal of Physiology, 119, 352-353.

LeDoux, J.E. (1992). Emotion and the amygdala. In Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, New York: Wiley-Liss, Inc., pp.339-351.

Leech, C.K., & McIntyre, D.C. (1976). Kindling rates in inbred mice: An analog to learning? Behavioral Biology, 16, 439- 452.

Lennox, H. (1991). Fast and slow kindling rat strains in vitro response of pyriform and perirhinal cortex to magnesium-free perfusate. Unpublished master's thesis, Carleton University, Ottawa.

Lester, D. (1968). Two tests of a fear-motivated theory of exploration. Psychonomic Science, 10, 385-386.

Liang, K.C. & Davis, M. (1990). Intra-amygdala injection of N-methyl-D-aspartate receptor antagonists impairs memory in an inhibitory avoidance task. Society for Neuroscience Abstracts, 16, 767.

Liang, K.C., Juler, R. & McGaugh, J.L. (1986). Modulating effects of post-training epinephrine on memory: involvement of the amygdala noradrenergic system. Brain Research, 386, 125-133.

Luders, H. & Lesser, R. (Eds.). (1987). Epilepsy: Electroclinical Syndromes, New York: Springer-Verlag.

Maclean, P.D. (1949). Psychosomatic disease and the "visceral brain": Recent developments bearing on the Papez theory of emotion. Psychosomatic Medicine, 11, 338-353.

Margerison, J.H. & Corsellis, J.A.N. (1966). Epilepsy and the temporal lobes: A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. Brain, 89, 499-530.

Masland, R.L. (1974). The classification of the epilepsies. In Vinken, P.J. & Bruyn, G.W. (Eds.), The Epilepsies:

Handbook of Clinical Neurology, Amsterdam: North-Holland Publishing Co.

- McAllister, W.R. & McAllister, D.E. (1971). Behavioral measurement of conditioned fear. In Brush, F.R. (Ed.), Aversive Conditioning and Learning, New York: Academic Press, pp.105-179.
- McLeod, W. (1993). Unpublished Master's thesis, Carleton University.
- McIntyre, D.C. (1978). Amygdala kindling and muricide in rats. Physiology and Behavior, 21, 49-56.
- McIntyre, D.C. (1979). Effects of focal vs. generalized kindled convulsions from anterior neocortex or amygdala on CER acquisition in rats. Physiology and Behavior, 23, 855-859.
- McIntyre, D.C., Dufresne, C., Kelly, M.E. & Mohapel, P. (1992). Kindling characteristics and susceptibility to status epilepticus of various temporal lobe structures Society for Neuroscience Abstracts, 18, 906.
- McIntyre, D.C. & Molino, A. (1972). Amygdala lesions and CER learning: Long term effect of kindling. Physiology and Behavior, 8, 1055-1058.
- McIntyre, D.C. & Reichert, H. (1971). State-dependent learning in rats induced by kindled convulsions. Physiology and Behavior, 7, 15-20.
- McNamara, J.O., Bonhaus, D.W., Shin, C., Crain, B.J., Gellman, R.L., & Giacchino, J.L. (1985). The kindling model of epilepsy: A critical review. CRC Critical Reviews in Clinical Neurobiology, 1, 341-391.
- Miserendino, M.J.D., Sananes, C.B., Melia, K.R. & Davis, M. (1990). Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature, 345, 716-718.
- Molino, A. & McIntyre, D.C. (1972). Another inexpensive headplug for the electrical recording and or stimulation of rats. Physiology and Behavior, 9, 273-275.
- Morrell, F. (1979). Human secondary epileptogenic lesions. Neurology, 29, 558.
- Mos, L.P., Royce, J.R. & Poley, W. (1973). Effects of postweaning stimulation on factors of mouse

- emotionality. Developmental Psychology, 8, 229-239.
- Mowrer, O.H. (1947). On the dual nature of learning - a re-interpretation of "conditioning" and "problem-solving". The Harvard Educational Review, 17, 102-148.
- Nieminen, S.K., Sirvio, J., Teittinen, K., Pitkanen, A., Airaksinen, M.M., & Riekkinen, P. (1992). Amygdala kindling increased fear-response, but did not impair spatial memory in rats. Physiology and Behavior, 51, 845-849.
- Ossenkopp, K. & Sanberg, P.R. (1979). Relationship of some open-field behaviors to amygdaloid kindled convulsions in Wistar rats. Physiology and Behavior, 23, 809-812.
- Peele, D.B. & Gilbert, M.E. (1992). Functional dissociation of acute and persistent cognitive deficits accompanying amygdala-kindled seizures. Behavioural Brain Research, 48, 65-76.
- Pellow, S., Chopin, P., File, S.E., & Briley, M. (1985). Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. Journal of Neuroscience Methods, 14, 149-167.
- Penfield, W. (1954). Temporal lobe epilepsy. British Journal of Surgery, 41, 1-7.
- Penfield, W. & Jasper, H. (1954). Epilepsy and the Functional Anatomy of the Human Brain, Boston: Little, Brown.
- Phillips, R.G. & LeDoux, J.E. (1992). Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behavioral Neuroscience, 106, 274-285.
- Pinel, J.P.J., Mucha, R.F., Phillips, A.G. (1975). Spontaneous seizures generated in rats by kindling: A preliminary report. Physiological Psychology, 3, 127-129.
- Pinel, J.P.J., Treit, D. & Rovner, L.I. (1977). Temporal lobe aggression in rats. Science, 197, 1088-1089.
- Post, R.M. (1983). Behavioral effects of kindling. In Parsonage, M. (Ed.), Advances in Epileptology: XIVth Epilepsy International Symposium, New York: Raven Press, pp.173-180.
- Post, R.M. & Kopanda, R.T. (1976). Cocaine, kindling and

- psychosis. American Journal of Psychiatry, 133, 627-634.
- Prince, D.A. (1978). Neurophysiology of epilepsy. Annual Review of Neuroscience, 1, 395-415.
- Racine, R.J. (1972a). Modification of seizure activity by electrical stimulation: I. After-discharge threshold. Electroencephalography and Clinical Neurophysiology, 32, 269-279.
- Racine, R.J. (1972b). Modification of seizure activity by electrical stimulation: II. Motor seizure. Electroencephalography and Clinical Neurophysiology, 32, 281-294.
- Racine, R.J. (1978). Kindling: The first decade. Neurosurgery, 3, 234-252.
- Reynolds, E.H. (1981). Biological factors in psychological disorders associated with epilepsy. In Reynolds, E.H. & Trimble, M.R. (Eds.), Epilepsy and Psychiatry, Edinburgh: Churchill Livingstone, pp.264-290.
- Royce, J.R. (1977). On construct validity of open-field measures. Psychological Bulletin, 84, 1098-1106.
- Seggie, J. (1971). Effect of adrenalectomy or gonadectomy on affective behavior changes following septal lesions in the rat. Journal of Comparative and Physiological Psychology, 74, 11.
- Slotnick, B.M. (1973). Fear behavior and passive avoidance deficits in mice with amygdala lesions. Physiology and Behavior, 11, 717-720.
- Smith, A. (1993). Unpublished observations.
- Spiers, P.A., Schomer, D.L., Blume, H.W. & Mesulam, M.-M. (1985). Temporo-limbic epilepsy and behavior. In Mesulam, M.-M. (Ed.), Principles of Behavioral Neurology, Philadelphia: F.A. Davis, pp.756-776.
- Sramka, M., Sedlak, P., & Nadvornik, P. (1977). Observation of kindling phenomenon in treatment of pain by stimulation in the thalamus. In Sweet, W.H. (Ed.), Neurosurgical Treatment in Psychiatry, Pain, and Epilepsy, Baltimore: University Park Press, pp.651-654.
- Stark-Adamec, C. & Adamec, R.E. (1986). Psychological methodology versus clinical impressions: Different perspectives on psychopathology and seizures. In Doane,

- B.K. & Livingston, K.E. (Eds.), The Limbic System: Functional Organization and Clinical Disorders, New York: Raven Press, pp.217-227.
- Steingart, M.O. (1983). The selective breeding of seizure-prone vs. seizure-resistant rats based on amygdaloid kindling: Behavioral, electrophysiological and pharmacological measures. Unpublished doctoral dissertation, McMaster University, Hamilton.
- Stone, W.S. & Gold, P.E. (1988). Amygdala kindling effects on sleep and memory in rats. Brain Research, 449, 135-140.
- Strauss, E. (1988). Ictal and interictal manifestations of emotions in epilepsy. In Boller, F. & Grafman, J. (Eds.), Handbook of Neuropsychology, Amsterdam: Elsevier/North-Holland Publishing Co.
- Taylor, D.C. & Lochery, M. (1987). Temporal lobe epilepsy: Origin and significance of simple and complex auras. Journal of Neurology, Neurosurgery and Psychiatry, 50, 673-681.
- Temkin, O. (1971). The Falling Sickness Baltimore & London: John Hopkins Press.
- Terzian, J. & Ore, G.D. (1955). Syndrome of Klüver and Bucy. Neurology, 5, 373-380.
- Tsuboi, T. & Okada, S. (1985). The genetics of epilepsy. In Sakai, T. & Tsuboi, T. (Eds.), Genetic Aspects of Human Behavior, Tokyo: Igaku-Shoin, pp.113-127.
- Walsh, R.N. & Cummins, R.A. (1976). The open-field test: A critical review. Psychological Bulletin, 83, 482-504.
- Weiskrantz, L. (1956). Behavioral changes associated with ablation of the amygdaloid complex in monkeys. Journal of Comparative and Physiological Psychology, 4, 381-391.
- Welker, W.I. (1957). Free versus forced exploration of a novel situation by rats. Psychological Reports, 3, 95-108.
- Williams, D. (1956). The structure of emotions reflected in epileptic experiences. Brain, 79, 29-67.
- Zaide, J. (1974). Differences between Tryon Bright and Dull rats in seizure activity evoked by amygdala stimulation. Physiology and Behavior, 12, 527-534.

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