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**The Effects of Amygdala Kindling on
T-maze Performance in Epileptogenically Fast
and Slow Kindling Rat Strains**

by

Wayne S. McLeod

A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of
the requirements for the degree of

(Master of Science)

Department of Psychology

**Carleton University
Ottawa, Ontario
December 20**

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The Effects of Amygdala Kindling on T-maze Performance in Epileptogenically Fast and Slow Kindling Rat Strains

submitted by

Wayne S. McLeod

in partial fulfilment of the requirements
for the degree of Master of Science

Chair, Department of Psychology

Thesis Supervisor

Carleton University
1994-95

Abstract

The present study investigates acute versus chronic effects of amygdala kindling and kindling induced seizures on both working and reference memory performance in genetically epilepsy resistant (SLOW) and epilepsy prone (FAST) rat strains. Rats from each strain were trained to high levels of performance in the T-maze on a delayed nonmatch-to-sample (DNMS) and stem discrimination task prior to kindling stimulations. Performance was monitored 23 hours after daily stage 1,2,3,4 and 5 amygdala kindled convulsions and also 1 hour and 10 minutes after stage 5 convulsions in fully kindled animals. After a stimulation free period, fully kindled animals were retested (without restimulation) with increased intratrial delays of 2,3 and 5 minutes on the DNMS task. The results indicated that working but not reference memory performance of the SLOW strain was better before kindling and was also less susceptible to kindling perturbation (from stage 5 seizures) than the FAST strain at all phases of maze testing. Implications for possible neuropharmacological differences in limbic areas that may account for disparaging memory performance of epilepsy resistant versus epilepsy prone strains of rats are discussed.

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Appendix B. Contains the details of individual data analysis for specific sections of the latency results.

Introduction

Epilepsy

Some of the earliest records in the history of man contain descriptions of individuals who suffered from epileptic seizures. Descriptions date back to 17th century B.C. in the papyri stone tablets of ancient Egypt (Thornton, 1976) and in *The Yellow Emperor's Classic of Internal Medicine* (770 -220 B.C.) of early China (Lai & Lai, 1991). The name *Epilepsia* is from the Greek for "a taking hold of from above" (*epi* = from above, *leptos* = to grasp hold of). To the ancient Greeks it was "the sacred disease" because those who had epilepsy were thought to be favoured by the gods, and endowed with the gift of prophecy.

Today, epilepsy is identified as the second most common neurological disorder next to stroke, affecting about 1% to 3% of the world population (Martin, 1991). The high prevalence may be because of the diversity of etiological factors such as head injury, poisoning, drugs, drug or alcohol withdrawal, metabolic disturbances, hyperthermia, or infectious diseases. The diagnostic hallmark of epilepsy is the recurrence of seizures that manifest most often as overt behavioral convulsions. They vary according to type and severity, such as the grand mal or the complex partial type. Unconsciousness invariably accompanies grand mal seizures, but not necessarily complex partial seizures. Conversely, the "absence" seizure will often manifest as a brief interruption in the stream of consciousness, perhaps accompanied with no more

than atypical blinking of the eyelids.

Brain damage is readily inferred from the observance of an epileptic seizure. Normal brain functions such as perception, thinking and memory are suspended, rendering epileptics incognizant and amnesic for events surrounding the rhythmic or "ictal" periods. A well known clinical entity is the period immediately following ictus, referred to as the post-ictal state, or post-ictal depression (Devinsky & Bear, 1991). This state, is often characterized by confusion, disorientation, temporary memory loss, irritability, tiredness, moodiness, and depression. Cognitive functions are profoundly impaired during ictus or post ictus, but numerous studies also suggest the presence of less conspicuous permanent cognitive impairments that persist between ictal episodes, in what is referred to as the interictal state (Berent et al., 1986).

Whether a direct or indirect result of seizures, the cognitive, emotional and psychosocial impairments in epileptics are considerable, even when compared to populations with other medical problems (e.g., asthma or diabetes; Hoare, 1984; Mathews, Barabas, & Ferrari, 1982). Seizure variables such as age of onset, seizure type, laterality of focus, and seizure frequency all shape the nature and the severity of cognitive impairment (Seidenberg, 1989 for a review). The most common deficits include slower reaction time (Brown, Penry, Porter, & Dreifuss, 1974), attentional deficits (Hermann & Seidenberg, 1989) and memory impairment (Gallassi, Morreale, Lorusso, Pazzaglia, & Lugaesi, 1988). Of these and other cognitive impairments, memory problems are among the most commonly reported complaints.

Memory

To remember is to live.

Martin Buber

Martin Buber eloquently captures how fundamentally important memory is to our sense of being and quality of life. Basically, memory can be defined as the ability to consciously remember past experiences or previously learned information (LeDoux, 1993). Usually it is taken for granted and its importance only becomes apparent when, as in Alzheimer's disease, it is compromised. In Martin Buber's colloquial impression, memory is experienced and conceptualized as a unitary global cognitive phenomenon.

It is now widely acknowledged in research that there is a high degree of functional specificity in the brain (Gazzaniga, 1989). Multiple memory systems are believed to represent many different types of memory capacities (Thompson, 1993). Some classificatory divisions include episodic versus semantic, procedural versus declarative, working versus reference, dispositional versus representational verbal versus spatial and emotional versus nonemotional (Squire, 1988;1992; Thompson, 1986; LeDoux, 1993). Of these, working versus reference is a division that commonly applies to animal studies that use rats.

Working and Reference Memory

A conventional means of referring to memory in various animal studies is to classify memory into working and reference components (Honig, 1978; 1990; Olton, 1978; Olton, Becker & Handelmann, 1979). Working versus reference memory is operationally defined as single trial distinct versus multi-trial memory for information necessary to performing a particular task. In other words, working memory holds critical information within a single trial while reference memory holds information that is useful across many trials. One way of distinguishing between working and reference memory is with respect to the duration of information storage. Presumably, the information in working memory pertain to recent events of transient importance, that is stored for a limited time, and is highly vulnerable to interference effects compared to reference memory (Honig, 1978; 1991; Olton, Becker & Handelmann, 1979). For example, lower performance occurs in delayed non-match-to-sample (DNMS) tasks where the intertrial delay exceeds the span of working memory. Delays may also be imposed on the working memory task for the radial arm maze with similar results for rats (Olton, Becker & Handelmann, 1979; Benninger, et al., 1986). The findings are consistent with the human literature which shows that long-term structural (reference) memories are less disrupted by brain traumas compared to shorter-term (working) memories (Baddeley, 1990; McCarthy & Warrington, 1991;

Squire, 1988).

Reference memories are further distinguishable on the basis of showing a consolidation gradient; they become less susceptible to disruption over time (McGaugh & Dawson, 1971). Working memories, on the other hand, do not show this gradient (Knowlton, McGowan, Olton, & Gamzu, 1985, Olton & Wolf, 1981). This is consistent with the observation that rats acquiring maze tasks initially make many reference memory errors before they learn to stay out of unproductive areas (reference memory), whereas working memory errors are minimal from the onset (Honig, 1991). With the exception of some species of birds (Clark's Nutcrackers) with very long working memory intervals (Kamil & Balda, 1985), reference memory usually has longer memory intervals compared to working memory. Therefore, this is one method of distinguishing between the two.

Empirical evidence suggests that the two kinds of memory processes are believed to be governed by partially independent neural mechanisms (Honig, 1991, for a review). Specifically, hippocampal impairment in rats results in working memory deficits but not for reference memory (Olton, 1979; Olton, Becker, & Handelman, 1979; Knowlton et al., 1989). Additionally, damage to both the amygdala and hippocampus impairs working memory on a delayed nonmatch to sample task (DNMS) more than either amygdala or hippocampal lesions in isolation. Also, damage to the basolateral amygdala nucleus also has shown to interfere with working memory but not reference memory (Ohno, Yamamoto & Watanabe, 1992; Ohno, Yamamoto & Watanabe, 1993). It is hypothesized that the working memory deficit

from amygdala lesions is the result of the lowering of central cholinergic function within the amygdala. Therefore, the empirical evidence suggests that working memory errors can result from limbic system damage.

Reference memory deficits in rats, on the other hand, have been shown to result from mediodorsal thalamic lesions (Stokes & Best, 1990). Limbic or hippocampal lesions that impair working memory have only mild effects on reference memory (Olton, Becker & Handelman, 1979; Thomas & Gash, 1988; Stokes & Best, 1990). In humans, retrograde amnesia which involves long-term, or reference type, memories occurs after alcoholic neurotoxicity, infarct or injury to diencephalic structures, particularly the mediodorsal thalamic nucleus (Victor et al., 1971; Squire & Moor, 1979; Markowitch, 1982; Ojemann and Dodrill, 1985; Squire, 1986, 1988; Zola-Morgan & Squire, 1990).

In summary, the working and reference memory have at least partially independent neural mechanisms that account for their observable differences. Thus, the type of memory that is impaired suggests a loss of function in those neural representations that support it. However, the extent to which working and reference memory share the same neuroanatomical space has yet to be determined.

The Amygdala and Memory

Traditionally, the amygdala is best known for its involvement in emotion functions (Aggelton & Mishkin, 1986; Richardson, 1973). Also, the

amygdala, independent of other structures, is known to play an important role in learning and memory of rats, monkeys, and cats (Sarter & Markowitsch, 1985, for a review). In primates, combined lesions of the amygdala and hippocampus produce a more profound memory impairment than either amygdala or hippocampal lesions in isolation (Mishkin, 1978; Murray & Mishkin, 1984; Squire, 1992). Evidence also suggests that the amygdala and hippocampus have distinct roles in the formation of memories. Put in succinct terms, the corticohippocampal system encodes information in the form of declarative representations (Eichenbaum & Otto, 1992; Squire, 1992; Alkon et al., 1992). The amygdala, on the other hand, is thought to modulate the storage of memories according to their affective components (Gold, 1989) via the influence of hormonal, adrenergic, GABAergic and opioid peptidergic systems (Gold, 1989; McGaugh, 1989; McGaugh et al., 1990; McLaughton, 1991). Put in other words, the amygdala is important for formulation of emotional memories.

Much evidence implicates the amygdala in the learning of highly arousing aversively motivated training situations that may or may not have fear components (Cahill & McGaugh, 1990; Gold, 1989). Supporting studies have found that amygdala lesions eliminate learning in highly aversive tasks such as conditioned taste aversion (Dunn & Everitt, 1988) active (Bush, Lovely, & Pagano, 1973) and passive shock avoidance (Dunn & Everitt, 1988; Pellegrino, 1968) or nictitating membrane response (Whalen & Kapp, 1991), stress-related tasks such as potentiated startle reflex (Hitchcock & Davis, 1986) and fear related tasks such as inescapable shock (Maier, 1993). This perspective is further supported by excitotoxic amygdala lesions

(produced by injection of N-methyl-D-aspartic acid) that impaired performance on a 1-trial aversive (foot shock) task (Cahill & McGaugh, 1990).

There is a growing consensus of evidence that different nuclei of the amygdala have different functional roles. The central nucleus (ACe) of the amygdala appears to be critical for the learning of simple associations of stimulus aversion in classical Pavlovian conditioning, such as the nictitating membrane reflex (Whalen & Kapp, 1991). Selective lesions to the ACe abolished the reflex in the aforementioned study. More specifically, the ACe was found to be involved in conditioning acquisition, but not retention of active and passive shock avoidance (Roosengaal, et al., 1993). However, classical conditioning of the nictating membrane reflex (NMR) can also be abolished by lesions of deep cerebellar nuclei when the ACe is intact (McCormick & Thompson, 1990). What, then is the unique contribution of the ACe to NMR conditioning? It is speculated that the widespread projections of the ACe to the brain stem (Schwaber et al., 1982; LeDoux, 1988), probably modulate the aversive "flavour" of memories associated with cerebellar learning.

There is ample empirical evidence that the amygdala is also involved in appetitive reinforcement (Goomas & Steele, 1980; Henke, Allen, & Davison, 1972; Henke & Maxwell, 1973; Peinado-Manzano, 1989; Pellegrino, 1968) and conditioning for tasks where previously neutral stimuli are paired with attractive substances that elicit approach (Baylis & Gaffan, 1991; Cador, Robbins, & Everitt, 1989; Everitt, Morris, O'Brien, & Robbins, 1991; Hiroi & White, 1990). The neural substrate for appetitive reinforcement appears to be distinct from that for negative reinforcement.

Damage to the ACe (Cahill & McGaugh, 1990) or deep cerebellar nuclei (Steinmenz, Long, & Miller, 1993) impair acquisition of an aversively motivated task but does not impair performance on appetitively motivated tasks. Instead, the basolateral and lateral nuclei have been found to be involved in appetitive reinforcement (Cador et al., 1989; Robbins et al., 1989; Everitt et al., 1991; Hiroi & White, 1991; Peinado-

- Manzano, 1989).

Taken together, the studies of amygdala function are consistent with the hypothesis that the brain is capable of acquiring different kinds of information through different, neural pathways that are more or less independent. The ACe and the basolateral and lateral nuclei are differentially involved in aversive vs appetitive motivation respectively. Large amygdala lesions that involve both nuclei are likely to result in a more general functional deficit for the acquisition of appetitive and aversive tasks.

Epilepsy and Memory

In the past brain research has greatly benefited from the study of the epilepsies and has lead to the formation of such concepts as the peri-Rolandic homonculus, hemispheric based models of cognition from commissurotomy patients, and the critical role of the temporal-lobe and hippocampus for cognitive memory (Novelly, 1992). The latter of these concepts was originally confirmed in what was an epilepsy-based surgical treatment. In 1953, the much noted case of patient H.M. who underwent

bilateral surgical temporal lobectomy for intractable epileptic seizures, was rendered with permanent amnesia (Scoville, & Milner, 1957; Corkin, 1984). Since then, temporal lobe epilepsy (TLE) has been instrumental in the formulation and development of material specific models of memory (Frisk & Milner, 1990; Loring, et al., 1989; Kolb & Wishaw, 1985).

TLE often gives rise to complex partial seizures and is the most common variety of epilepsy known (Engel, 1989). Due to the involvement of the temporal lobe in learning and memory, it would come as no surprise that epileptics with TLE show memory impairment on neuropsychological exam. However, even when heterogenous groups of epileptics are tested, neuropsychological examination shows epileptics to have poorer memory performance than non epileptics (Dodrill, 1992). The epileptics in this study had fairly good seizure control and the testers were confident that each subject was in an interictal state. However, epileptics tend to do well on tasks that require the use of well established long-term cognitive skills, such as reading comprehension (Dodrill, 1992). Well established long term skills in humans could be regarded as the analog of reference memory for animals. Therefore, it could be inferred that epileptics with good seizure control who are in the interictal state show good preservation of long-term or reference type memories.

The average person is likely to encounter small, everyday memory tasks that are important for the moment but are forgotten by the next day. These transient memory tasks are analogous to the types of working memory tests in animal studies. A heterogenous sample of epileptics with good seizure control were given the type of

test which tapped these types of everyday working memory tasks in response to complaints from epileptics of everyday memory failures (Dodrill, 1992). The results indicated that the epileptics underestimated the extent of their memory failures for these tasks. This suggests that the neural substrate of working memory may be particularly vulnerable to disruption in epileptics, even in the interictal state. One possible explanation is that subclinical or "silent" interictal discharges which cause a transitory cognitive impairment (TCI) of brief duration (Binnie & Marston, 1992; Dodrill, 1992), may be responsible for the working memory impairment. TCI has been shown to disrupt working memory (Hutt & Gilbert, 1980) and short term memory (Binnie et al., 1987) tasks.

Kindling

Kindling refers to the progressive increase in epileptiform activity and long lasting seizure susceptibility in animals. It is widely acknowledged as an adequate model for the study of human epilepsy (Goddard, McIntyre & Leech, 1969; Pinel et al., 1975; McNamara, 1986; McIntyre & Racine, 1986; Adamec, 1990; Sato, et al., 1990). One ideal method of evoking the process is by repeated low voltage electrical stimulation via chronically implanted electrodes of certain brain areas once or twice daily (Racine, 1978). As an experimental animal model of epilepsy, kindling has

many advantages over other models (Goddard et al., 1969; Racine & Burnham, 1984). It reliably produces chronic epileptogenesis and offers tight experimental control over seizure onset and duration without the side effects of chemical lesion models.

The kindled brain shows a number of physiological alterations at, but which are not limited to, the site of stimulation (Sato et al., 1990). It is only reasonable that these kindling induced changes result in some physiological and behavioral consequences. The most obvious of which are a progressive increase in electrographic epileptiform activity induced by the delivery of periodic kindling stimulations. The electrographic activity, or afterdischarge (AD) occurs in parallel with the development of 5 stages of seizure responses (Racine, 1972). The behavioral changes that parallel AD development consist initially of automatisms of the facial musculature (Facial clonus; Stage 1) but then progress to facial clonus with larger movements such as rhythmic head bobbing (Stage 2) then facial clonus, head bobbing and forelimb clonus (Stage 3); facial clonus, head bobbing, rearing with forelimb clonus (Stage 4); finally facial clonus, head bobbing, forelimb clonus, rearing with loss of postural control (Stage 5). These effects of kindling are quite permanent and transynaptic, lasting when animals are left unstimulated for extended periods of time (Goddard et al., 1969; Racine, 1978).

Kindling and Memory

Amygdala kindled seizures produce learning and memory deficits in a variety of emotion-based tasks. Deficits have been reported for passive avoidance learning in bilaterally kindled, electrically stimulated rats (Peele & Gilbert, 1992). Similarly, bilaterally convulsed unilaterally stimulated amygdala kindled rats were rendered amnesic for a conditioned emotional response (CER) paradigm (McIntyre, 1970). Direct comparisons between convulsions from amygdala kindling versus convulsions from cortex of rats showed a deficit for CER learning in the former animals but not the latter (McIntyre, 1969). Therefore the acquisition of emotion-based learning tasks appear to be sensitive to seizures from the amygdala but not anterior frontal cortex.

Amygdala kindling induced seizures are not limited to impairing emotion-based tasks and have been found to impair spatial reference memory in rats when tested in the hole board (Beldhuis, 1992,a;1992,b), and place learning in the Morris water maze (McNamara et al., 1992). Spatial memory in rats is thought to be mainly processed by the hippocampus (Barnes, 1989, O'Keefe & Nadel, 1979) and hippocampal kindling induced seizures disrupt spatial memory (Cain et al., 1993; McNamara et al., 1993). How amygdala kindled convulsions result in spatial memory impairments is not precisely known. The reference memory impairment in the hole board test was found to be related to amygdala kindled convulsions that elevate protein kinase C activity on the Mu cholinergic receptor subtype in the dentate gyrus and CA1 subfields of the hippocampus (Beldhuis et al., 1992,a; 1992,b). Therefore, the disruption of the normal

cholinergic receptors of the hippocampus may constitute a functional lesion as a result of amygdala kindled convulsions. This design did not consider, however, whether amygdala kindling *per se* without the induction of seizures was sufficient to cause a spatial memory impairment.

The cognitive impairment induced by ictal events from amygdala kindled animal models appears to mimic the conspicuous, cognitive impairment of epileptic humans in ictus or immediately post-ictus. A second stage of testing involves the assessment of the interictal state for cognitive impairment in kindled animals. Cognitive deficits in the interictal state are more difficult to demonstrate in kindled animals. Indeed, when fully amygdala kindled rats were seizure free for two weeks, the impact on spatial learning was minimal (Nieminen et al., 1992). These findings were supported by another study which found that amygdala kindling without seizure induction did not produce spatial memory deficits (McNamara et al., 1992). Additionally, amygdala kindled rats were shown to acquire a two-way active avoidance task like non-kindled controls (Becker, et al., 1992). One possible explanation for these null findings is that in the absence of ictal activity, the functional lesion has only mild effects when the usual learning and memory tests are used for rats.

There is also evidence, however, that some cognition-related behavioral changes continue to persist for weeks long after the last kindling induced convulsion. This points to a cognitive impairment of a more permanent type, and may be related to underlying permanent changes in brain synapses and excitability. Bilateral, but not

unilateral amygdala kindling (independent of seizures) disrupted the acquisition of a fear-motivated conditioned emotional response (McIntyre & Molino, 1972), and passive avoidance learning (Peele & Gilbert, 1992; Stone & Gold, 1988; Boast & McIntyre, 1977). The aforementioned studies all showed a *learning* deficit in amygdala kindled rats compared to non-kindled or unilaterally kindled rats.

Hippocampal kindling has also been shown to result in impairments in radial arm maze performance for fully kindled (35 afterdischarges) rats (Leung, Boon, Kaihara, & Innis, 1990) and partially kindled (21 afterdischarges) rats (Leung & Shen, 1991) compared to control animals. These latter studies are important because they demonstrate a post-kindling *retention* failure for rats that acquired a high level of radial arm maze performance prior to being kindled. Whether amygdala kindling independent of seizures results in failures of retention for well learned maze tasks has received little experimental testing.

In summary, evidence of memory impairments exists in rats shortly after the induction of amygdala kindled seizures. There is also evidence of a less conspicuous chronic learning and memory impairment in kindled rats in the interictal state. Studies that show null results in the latter case, may be due in part to the lack of test sensitivity for what is a mild impairment during the interictal state. Also, it is not known whether amygdala kindling affects retention as well as learning acquisition for rats in the interictal state.

The Amygdala as a Kindling Site

Choosing the amygdala as the site of kindling has a number of advantages. It has a lower kindling threshold than many other brain areas and fewer kindling trials are needed to produce convulsive seizures than hippocampal kindling (Gilbert, 1988; Racine, et al., 1977; McIntyre & Plant; 1990). Depending on the area, the hippocampus may kindle three to six times slower than the amygdala or other structures of the temporal lobe (Racine, Rose & Burnham, 1977). Another reason is the permanent nature of amygdala kindling. Although the hippocampal kindled animal receives much more stimulation, the kindled seizure often reverts back to weaker forms and cannot always be reliably evoked (Racine, 1991). The tissue in the amygdala and piriform cortex is among the most sensitive for the development of the chronic epileptogenic state (Kairiss, et al., 1984; Racine, et al., 1988). Such sites that are the most susceptible for epileptogenesis and seizure formation in animal models probably have similarly epileptogenic tendencies in the analogous structures (i.e., amygdala, olfactory bulb or other limbic areas) for humans. In support of this is the clinical observation that the amygdala is a critical structure in the pathogenesis of temporal lobe epilepsy, and is one of the most common sites for the genesis of epileptiform activity and complex partial seizure onset (Gloor, 1992). Therefore, amygdala kindling serves as an ideal animal model for the study of human temporal lobe epilepsy.

Genetic Models of Epilepsy

There is much evidence implicating genetic factors as strong determinants that predispose humans to epilepsy and seizure development (Delgado-Escueta, White, Greenberg, & Treiman, 1986). Over, 141 single gene disorders have been identified as increasing the risk of seizures in people (Anderson et al., 1986). Also, there is overwhelming evidence of a genetic predisposition for the absence epilepsies (Porter, 1993). Estimates from twin studies put correlations between monozygotic sibs at rates as high as 60% and dizygotic pairs at 13% (Tzuboi & Okada, 1985). Studies that employ DNA markers have found at least three genetic based epilepsies mapped to specific chromosomes: benign familial neonatal convulsions, juvenile myoclonic epilepsy and Baltic progressive myoclonic epilepsy (Treiman, 1993, for a review). Unfortunately, the genetic epilepsies have heterogenous clinical phenotypes and are variably penetrant age dependent disorders. Therefore, there are difficulties in the diagnosis and tracking the incidence of these epilepsies within a population.

Genetic animal models of human epilepsy are a instrumental in facilitating the understanding of the genetic basis of epilepsy in humans. A comprehensive review describes a number of genetic animal models from different species as sharing many features in common with human epilepsy (Buchalter, 1993). The diversity of animal species used as models include baboons, dogs, cats, rats, Mongolian gerbils, mice and fruit flies (Fisher, 1989). These models offer a nervous system that is already abnormal without perturbation. An added advantage is the tight experimental control

over the background genetics, thereby eliminating other disorders which make the interpretation of experimental results problematic.

One of the most useful animal models of epilepsy is the genetically epilepsy-prone rat (GEPR; Faingold, 1988). The model has provided insights into the neuroanatomy of audiogenic seizures arising within the inferior colliculus, plus anticonvulsant sensitivity of seizing rats to standard epilepsy prophylactics, and alterations in the levels of various neurotransmitters (Buchalter, 1993). GEPR rats were derived from the Sprague-Dawley strain of rats that were bred for their susceptibility to sound (Consroe et al., 1979). Immature GEPR rats show learning and memory impairments on tasks such as the T-maze and water maze even after only brief seizure exposure (Holmes et al., 1990). Unfortunately, little is known about learning and memory capacities of the GERP rats in comparison to the original Sprague-Dawley line.

FAST and SLOW Rat Strains

In addition to genetic animal models for epilepsy that were already mentioned, we have the FAST and SLOW rat strains that were developed from parent strains of the Long-Evans Hooded rats and Wistar rats (Steingart, 1983). The two strains were developed over 10 generations on the basis of amygdala kindling rates; by then FAST

rats required an average of 11 kindling stimulations to reach the first stage 5 kindled convulsion, whereas SLOW rats required an average of 41.1 kindling stimulations. Hence the FAST rats are considered to be more epilepsy-prone than the SLOW strain, which are epilepsy-resistant based on the rate of evolution of electrographic and behavioral epileptiform activity.

The two strains differ on a number of behavioral, neurochemical and electrophysiological measures (Steingart, 1983, Dufresne, 1990; Lennox, 1991; Mohapel, 1993). Both strains appeared to learn a one way avoidance task well enough, but the SLOW rats exhibited strong freezing, and probably needed more time on the retention test to perform as well as the FAST rats (Mohapel, 1993). Therefore, it was thought that the SLOW rats manifested greater fear-emotionality and tended to exhibit immobility in response to negatively arousing stimuli. The SLOWs, however, tended to outperform the FASTs on less aversive tasks: the Morris water maze (Armstrong & McIntyre, 1992) as well as on appetitive tasks: the radial arm maze (Smith, 1993). Performance on another appetitive task: the T-maze favours the SLOW strain over the FAST (pilot study).

T-Maze Apparatus

The T-maze has been used extensively to study memory in neurobehavioral studies (Handelmann & Olton, 1981; Stanton, Thomas, & Brito, 1984; Thomas, 1979).

The T-maze appears to reveal the same neural and behavioral capacities in the rat as the radial arm maze and has the added advantage of simplicity. Reference memory can be assessed by rewarding an animal for choosing the same arm, or by a simple stem discrimination where the animal chooses the left or right alley across all trials. Working memory is most often assessed using a delayed nonmatch-to-sample (DNMS) where a rat is reinforced for choosing the arm opposite to the arm that last had the reinforcer. Rats can acquire the nonmatch-to-sample rule in the T-maze with little difficulty, making it an ideal test for working memory.

There are several reasons why the T-maze and DNMS task can be considered a good test for assessing the effects of kindling and kindling induced seizures on memory. The DNMS task is sensitive to limbic impairment, particularly combined lesions of the amygdala and hippocampus (Murray & Mishkin, 1983). Working and reference memory can be independently measured in the T-maze, and appear to have a different ontogeny (Green & Stanton, 1989). Infant rats are able to perform reference memory tasks at ages 15-21 days but are not able to learn working memory tasks (DNMS) until at least from 21-27 days of age. It is believed that the difference is because reference memory tasks are not as dependent on maturation of limbic structures as are working memory tasks like the DNMS (Green & Stanton, 1989). Thus the T-maze may be used to study limbic and non-limbic types of memory, which may correspond to working and reference memory, respectively.

Purpose

In this study we planned to look at the impact of amygdala kindling on the working and reference memory performance of our genetically epilepsy resistant (SLOW) and epilepsy prone (FAST) rat strains. In view of possible strain differences for working and reference memory prior to kindling, determining the baseline learning ability of the 2 strains was considered necessary. To achieve this, the strains were trained to high levels of memory performance before being kindled from the amygdala. Therefore memory performance was measured before, during and after kindling.

Given that working memory is sensitive to limbic system perturbation, it was first predicted that working memory would be more affected by amygdala kindling than reference memory in both strains. Secondly, the amygdala of the FAST strain has greater excitability than that of the SLOW strain. As such, the rate and extent of epileptiform propagation from the amygdala of FAST rats should evolve more rapidly to involve other limbic areas implicated in task performance. This same change was expected to take place at a slower rate for the SLOW strain. Therefore, the epilepsy prone FAST rats were predicted to show a greater memory impairment than the SLOW strain. Since it was not known just where and when (or if) the memory impairment would be manifested, memory was tested daily from the first day of kindling until the end of kindling where seizure severity reached stage 5 levels.

We also expected that the period of acute memory impairment following a

seizure (the post-ictal state) would be longer in the epilepsy prone FAST strain. This post-ictal vulnerability to memory disruption might be demonstrated by varying the time interval between the induction of a seizure and maze running, e.g., from 23 hours 1 hour and to 10 minutes between a seizure and learning. Thus we predicted that shorter intervals between a seizure and the maze running would produce more memory or performance problems.

Finally, it was predicted that kindling, independent of seizures would result in a potentially inconspicuous chronic working memory impairment. Thus the last stage of testing assessed this potentially subtle memory impairment in kindled animals by testing memory after the animals had been unstimulated for an extended period (10 days). Since a chronic memory impairment was expected to be subtle, we felt it might be better demonstrated by increasing the difficulty level of the working memory task. This was achieved by incrementally increasing the intertrial interval from 1 minute to 2,3 and then 5 minutes. Thus the longer delays were expected to unmask subtle memory deficits.

Method

Subjects

Twelve experimentally naive female Long-Evans X Wistar SLOW rats, and twelve experimentally naive female Long-Evans X Wistar FAST rats 180-250g were used. They were housed in groups with food (rat chow) and water *ad libitum*. The rats were maintained on a 12:12 light dark cycle prior to surgery and maze habituation and task acquisition. After surgery, the animals were housed singly in hanging cages. The animals were reduced to and maintained at 85% of their free feeding body weight prior to and for the duration of the T-maze learning procedures. To account for natural growth, the animals were allowed to gain 2-3 grams biweekly by adjusting the portion of food intake upward until the rats showed weight gain.

Surgery

The identical surgical procedure was performed on all rats prior to maze habituation and maze learning regardless of group assignment. Subjects were anesthetized with sodium pentobarbital (Somnotol; 60 mg/Kg, i.p.) and implanted with bipolar stimulation/recording electrodes made from twisted 0.127 mm Diamel-insulated Nichrome wire bilaterally in both amygdalae using the stereotaxic coordinates 0.2 mm posterior to bregma, 4.5 mm lateral to the midline and 8.2 mm below the skull surface. A ground wire was inserted over the frontal pole for recording EEG. Dental

cement and seven jeweller screws were used to fix the electrode and ground wire into position on the cranium. The electrode and ground pins were then inserted into a plastic headplug, which was held to the cranium with dental cement.

Apparatus

The T-maze was constructed of grey opaque plexiglass with a clear cover studded with breathing holes. The start box and two goal boxes measured 30 by 20 cm wide and 15 cm high. The main alley was 60 cm long and 20 cm wide. A partition divided the main alley into left and right corridors. When the goal box guillotine doors were lifted, a curtain at the front of the partition hid the corridors from visual inspection by the rat. Behind the curtain a sponge was used for sealing off one corridor at a time for learning the reference memory task.

The two arms of the maze measure 25 cm long and 20 cm wide. Guillotine doors separated the entrances to each of the goal boxes and were controlled by a string and pulley system suspended from the ceiling. The walls of the maze were 12 cm in height. A 2.5 cm diameter plastic food dish was located at the distal end of each goal box. The entire apparatus was situated on three legs 1 m above the floor in a room with fluorescent lighting and numerous extra-maze cues (see figure 1).

Figure 1. A schematic representation of the T-Maze apparatus.

Procedure

Maze Acquisition

Rats were weighed each day and given 10 - 12 g of Standard Lab Rat Chow. Also their weight was monitored until their weight was reduced to 90% of their free feeding body weight. As the rats were not fully matured at this age (approx 3 months) their weight was allowed to increase by approx 2 g every two weeks to account for some growth. Half of the FAST and SLOW rats were then randomly assigned to either the kindled or the non-kindled group.

The rats were given their first exposure to the maze (maze habituation) for 5 min on each of three consecutive days. During maze habituation, the guillotine doors were always open. Kellogg's Frootloops initially were scattered over the entire maze floor but were placed increasingly toward and in the goal arms and boxes by day three. Thus the animals' behaviour was shaped to anticipate a frootloop in the goal box only. After completion of maze habituation, the subjects received one training session each day, 5 days a week. Maze training and testing were done at approximately the same time each day during the light cycle for all subjects.

Learning Trials

In the first phase of the experiment, learning trials established baseline working and reference memory performance for each strain. The question of strain differences in memory performance before perturbation of the brain by kindling was assessed.

Each daily session consisted of 6 trials. A trial consisted of a working memory component and a reference memory component. The working memory component consisted of an information run and a choice run. The information run preceded the choice run on all trials. For the information run, one of the guillotine goal box doors was open while the other was closed. Both the open and closed goal boxes were baited with frootloops to balance for olfactory cues.

At the beginning of a trial, each rat was placed individually in the start box with its head oriented away from the guillotine door. The start box lid was then shut to prevent the animal from attending to the top edges of the maze. After 5 sec the door to the start box was opened and the rat was allowed to escape into the stem of the maze. The rat had to negotiate the stem of the maze by first passing under the curtain and second, finding which of either the left or right corridors was open and which was blocked. If the rat chose the blocked side, it was allowed to backtrack and enter the open side. After negotiating the stem successfully and reaching the maze arms, the rat was allowed to explore without interruption until it found the open goal box for the information run. The goal box was considered entered if the rat crossed over the guillotine door with all four paws. The guillotine door was then closed, and the rat was confined to the goal box and allowed one minute to eat the frootloop reinforcer. The rat was then returned to the start box for the beginning of the CR. The doors to both goal boxes were raised for the CR, and subsequently the rat was confined to the chosen goal box for 1 minute. For the CR, however, only one goal box was baited with a frootloop. The choice run baited goal box was opposite to the

baited goal box on the previous information run ; in other words, the correct choice run was a non-match to the information run . If the rat chose the baited goal box on the choice run (non-match) a correct choice was scored. On the other hand, if the rat chose the same goal box as on the information run (match), the choice was scored as an error. Correct choices, errors and latency (time per information run and CR) constituted the dependent measures for the maze task.

The reference memory task consisted of making the correct stem discrimination. Initially, all subjects were randomly assigned to training conditions with either a blocked left or right corridor in the stem. A particular subject had the same corridor blocked for all trials on all sessions. The curtain in front of the corridors prevented the subject from seeing which corridor was blocked. Equal numbers of left vs right corridors were blocked for each group. Since the rat must run down the stem twice, once for the information run and once for the choice run in a trial, there were twice as many reference memory choice trials as working memory choice trials. Learning sessions consisted of 6 trials per day for five consecutive days a week until correct responding reached 80% in both the reference and working memory tasks for two consecutive days.

Reaching criterion performance marked the second phase of maze learning. The goal in this phase was to document the impact of initial kindling on the memory performance of the now well trained rats. Half of the rats from each strain were selected to be kindled.

Each rat reached criterion levels of performance according to their own rate of

learning. When the criterion level was reached for a particular subject, it was randomly assigned to the kindled or the control group. The next subject to reach criterion performance was then assigned to the other group, opposite to the rat preceding it. Thus each group (kindled and control) had members that were relatively well matched in terms of maze acquisition rates.

For those rats assigned to the kindled group, maze performance was assessed 23 hours after each kindling, trial that reliably produced an afterdischarge (see below for kindling procedure). Kindling and maze trials continued for five days per week until all kindled animals had accumulated at least five generalized (Stage 5) kindled convulsions. The total number of maze trials for a control rat was matched with the total number of maze trials for a particular rat in the kindled group. After completion of this kindling phase, each animal was given one week rest prior to beginning the third phase of maze trials.

The third phase, is designed to examine whether the post-ictal state is associated with a cognitive impairment that extends for 1 hour after a fully generalized stage 5 seizure. The kindled rats experienced a fully generalized stage 5 convulsion and maze performance for working and reference memory was then tested 1 hour later. This procedure was repeated daily for 4 days.

A second part of phase 3 repeated the above procedure a second time over 4 days but the delay between each kindled convulsion and maze testing was reduced to 10 minutes. It was speculated that with this shorter time interval, both working and reference memory might be impaired in kindled animals.

In the fourth phase the long term or chronic effect of kindling on memory was determined. This phase questioned whether the kindled state could statically impair memory. To ensure that any residual effects of past seizures on memory was minimized, kindled animals were left seizure free for a 10 day rest before memory reassessment. No seizures were triggered during this phase of the experiment.

Subsequently, kindled and control rats were tested for a total of 6 trials each day for 5 days with a 1 minute delay between the information run and the choice run. This procedure was then repeated for 3 additional sets of 5 days, using delays of 2, 3 and 5 minutes between the information run and the choice run. These delays further challenged the working memory of the kindled and control rats.

Kindling

Rats that were kindled were exposed to a 2 sec 60 Hz sine wave stimulus train delivered to the left amygdala at an intensity sufficient to reliably produce an afterdischarge. The afterdischarge thresholds was determined on the first kindling day by stimulating with a low current (15 μ A, 25 μ A, 35 μ A, etc) that was progressively increased with 1 minute interstimulation intervals, until an afterdischarge was elicited. To minimize the transient or post-ictal after effects on maze performance all subjects were stimulated 23 hours prior to the learning session. The control rats were handled in a manner identical to the kindled group but did not receive electrical stimulation when placed into the kindling apparatus.

Histology

Upon completion of the fourth phase in the experiment, all rats were deeply anesthetized, and perfused with saline, followed by 10% formalin. The electrodes were removed 24 h later and the brain stored in 10% formalin for at least 3 days prior to sectioning. Frozen sections at 40 μ m, taken through the electrode tract, were mounted on slides, air dried, and stained with Cresyl Violet to confirm placement of the electrode tip in the vicinity of the amygdala.

Statistical Analysis

One way ANOVA was used to determine differences in kindling variables including kindling rates, convulsion latency, convulsion duration and afterdischarge duration between kindled SLOW and FAST rats. Two way ANOVA was used to determine between groups effects for strain (SLOW vs FAST) and group (kindled vs control) for all dependent variable maze measures (stem and arm discriminations and latencies). A two way MANOVA [task type (reference /working memory) vs group (control/kindled)] with repeated measures (latency and number of errors) were used to analyze the dependent measures across days. Simple effects tests were used where main effects and interactions were significant.

Results

Histology

One FAST rat and one SLOW rat lost head caps prior to full kindling. The data from these animals on all measures involving kindling was subsequently dropped from the experiment. One of the SLOW rats contacted a respiratory ailment and was dropped from the study. One FAST rat that reached full kindling lost head caps prior to the post-ictal depression testing in phase 3. One FAST rat lost its head cap during post-ictal depression testing. Some placements could not be confirmed from rats that lost head caps since the site of the electrode placement disappears with time if the rats are not euthanized shortly thereafter. This happened with two FAST rats and one SLOW rat that lost head caps but were kept in the experiment for participation in phase 4 of testing (which required no stimulation). In total the electrode placements were confirmed in the amygdala of 4 SLOW rats and five FAST rats in the kindled groups. Control animals were used whether or not the precise location of the electrode tip was in the amygdala.

Electrographic Measures

Figure 2 shows the afterdischarge (AD) durations for the first 17 days of kindling. Repeated measures analysis revealed that the SLOW strain had significantly shorter AD durations than the FAST strain $F(1, 13) = 16.6$, $p < .001$. The AD for both strains continued to increase over days as seen from a significant effect for days $F(16, 240) = 13.0$, $p < .001$. The AD duration of the FAST strain also increased significantly more rapidly compared to the SLOW strain as indicated by a strain X days interaction $F(16, 240) = 5.51$, $p < .001$. On later parts of the experiment, strain differences in AD duration were no longer significant.

The kindling rate was observed to be significantly more rapid for the FAST strain, which took fewer days ($\bar{x} = 13.8$) to reach full kindling than the SLOW strain ($\bar{x} = 39.4$), $F(1, 13) = 9.12$, $p < .01$.

Other kindling measures for convulsion latency and convulsion duration were not significant using ANOVA and MANOVA for a strain (Slow versus Fast) effect.

Behavioral Measures

The behavioral measures associated with learning the T-maze problem will be presented in 2 sections. First, a summary of the reference memory results will be followed by a more detailed summary of the choice run or working memory results for all 4 phases.

Figure 2. Mean ($\pm$ S.E.M.) of the AD duration (sec) evoked from electrical stimulation for the first 17 days of kindling.

Because the results section quickly became unnecessarily complicated, most of the latency results for both the information run and the choice run are not included in the results section but can be found in Appendix B.

Reference Memory Results

The results from the stem discrimination or reference memory test tended to be the same throughout all 4 phases of the experiment. As such, the reference memory data for individual groups and runs (information and choice) during the 4 phases will not be described. Rather a general overview of these results will be presented with representative examples. Most of the supporting statistics can be found in Appendix A.

In phase 1 of the experiment, there was no difference in the rate of acquisition of the stem discrimination between the strains. Figure 3 presents data from the first 10 days of maze learning for the information run part of maze learning. Repeated measures MANOVA showed no overall differences between the strains for learning the stem discrimination task over the first 10 days by a significant effect for DAYS $F(8, 160) = 27.4, p > .0001$, but no significant STRAIN x DAYS interaction. Therefore, the reference memory for the task was apparently acquired easily and with equal facility by both strains. Thus both strains easily learned the stem discrimination, and performed this behaviour with precision.

During phase 2 of the experiment, when kindling was initiated in the 2 strains, the kindling treatment 23 hours before each learning trial was also associated with no apparent differences in either strain. The results of each strain, with or without kindling, continued to be expressed exactly as depicted in Figure 3.

Subsequently, during phase 3, slight strain differences in reference memory expression appeared during the 2 post-ictal depression experiments. At the 1 hour post-ictal testing, as can be seen in Figure 4, the FAST strain performed more poorly than the SLOW strain, however, this effect was largely a result of the kindling influence in the FAST rats (see Appendix A for the detailed statistics). Nearly identical results for the 2 strains were observed at the 10 minute post-ictal period. Again the kindled FAST rats were inferior to all other groups (Figure 5 and Appendix A). Thus proactive effects of the recent convulsion (1 hour or 10 minutes) was slightly debilitating on reference memory in the FAST but not in the SLOW rats. On the other hand, a convulsion 23 hours before learning trials had no effect on reference memory in either strain.

Working Memory Results

Phase 1: Initial Training

Learning Trials

Unlike the earlier reference memory results that showed little difference between the strains, substantial choice run or working memory differences were

Figure 3. Mean ($\pm$ S.E.M.) correct choices for the first ten days of learning the T-Maze stem discrimination; SLOW and FAST rats. Scores for the stem discrimination on the information run were combined with those from the Choice Run for a maximum of 12 runs each day.

Figure 4. Mean ($\pm$ S.E.M.) correct choices for six daily stem discrimination trials per day. A stage-5 kindled convulsion preceded the daily session of trials by 1 hour, for each rat over 4 consecutive days.

Figure 5. Mean ($\pm$ S.E.M.) correct choices for six daily stem discrimination trials per day. A stage-5 kindled convulsion preceded the daily session of trials by 10 minutes, for each kindled rat over 4 consecutive days.

usually seen between the 2 strains. In Figure 6 repeated measures MANOVA analysis of arm discrimination performance (working memory) over the first ten days showed the SLOW rats ($\bar{x} = 4.4$) significantly exceeded the FAST rats in overall number of correct choices ($\bar{x} = 3.3$), $F(1, 18) = 27.1$ $p < .001$. It is apparent that the SLOWs learned at a much faster rate than the FAST rats, confirmed by a significant effect for performance over days $F(8, 160) = 2.7$ $p = .01$.

The total number of days for all the rats within each strain to reach at 80% correct responding for at least two consecutive days (criterion levels) is presented in Figure 7. For arm discrimination, the SLOW rats ($\bar{x} = 9.0$) took significantly fewer days than the FAST rats ($\bar{x} = 23.1$) to reach criterion performance $F(1, 20) = 46.5$, $p < .0001$. As such, the SLOW strain appeared to learn the working memory task much more quickly than did the FAST strain.

Phase II: Kindling Trials

Daily Kindling Sessions

Daily T-maze performance was recorded (Figure 8) 23 hours following daily kindling sessions over for the first 10 days of kindling. MANOVA analysis was done for the first 10 days only, because the kindled FAST rats reached full kindling quickly and so few were remaining past 10 days that group comparisons were problematic. The first 10 days showed that the SLOW rats generally ($\bar{x} = 5.17$) continued to outperformed the FAST rats [$(\bar{x} = 4.2)$, $F(1, 18) = 29.1$ $p < .001$], on the arm

Figure 6. Mean (+S.E.M.) correct arm discrimination choices for the first ten days of learning the T-Maze for SLOW and Fast rats. Days represent six arm discrimination trials for each rat.

Figure 7. Mean ($\pm$ S.E.M.) total number of days for all SLOW and FAST animals took to reach criterion levels of performance before proceeding to phase 2 kindling.

Figure 8. Mean correct choices for T-Maze arm discrimination performance 23 hours after kindling sessions for the first ten days. N = the initial number of animals in a group and a change to a lesser number as the animals complete their kindling.

discrimination task. In addition, there were no significant differences in arm performance between kindled and control groups. This is despite the fact that almost all FAST rats reached stage 4 to 5 kindled convulsions by day 10 while the kindled SLOWs were all at stage 2-3 kindled convulsions. Thus a convulsion 23 hours before a learning trial did not affect the working memory in the FAST rats.

Last Six Trials

To better compare the strains once kindled, learning following a stage 5 convulsion was looked at for six days. Figure 9 shows arm discrimination performance for the last six days of kindling for kindled and control animals seizure 23 hours prior to maze testing. Overall analysis of the performance summed over the six days showed a main effect for strain, where the SLOW rats ($\bar{x} = 5.2$) made more correct arm choices than FAST rats ($\bar{x} = 4.2$), $F(1, 17) = 38.2$, $p < .001$. There was also a main effect for group, where the kindled rats ($\bar{x} = 4.5$) had lower performance than the control group ($\bar{x} = 4.9$), $F(1, 17) = 5.1$, $p = .04$. There was also a significant strain X group interaction $F(1, 17) = 4.9$, $p < .05$, which was due to the lower maze performance of the kindled FASTs compared to the other groups that performed at or over criterion levels (80% correct). This was confirmed by simple effects tests that showed the significantly lower performance of the kindled FAST rats ($\bar{x} = 3.8$) compared to the control FAST rats ($\bar{x} = 4.6$), $F(1, 10) = 10.8$, $p < .01$, the kindled SLOW rats ($\bar{x} = 5.2$), $F(1, 8) = 27.4$, $p = .001$ and the control SLOW rats ($\bar{x} = 5.2$), $F(1, 7) = 26.9$, $p = .001$. There were no significant differences between kindled and

Figure 9. Mean ($\pm$ S.E.M.) correct choices for T-Maze arm discrimination preceded 23 hours by stage-5 kindled convulsions for the last six days of kindling.

control SLOWs. Thus the FAST rats continued to perform more poorly than the SLOW rats, and kindling further degraded performance, but only in the FAST strain.

Phase III: Post-ictal Depression Testing

One Hour Testing

When convulsions were triggered 1 hour before maze performance, several interesting outcomes occurred. Figure 10 shows arm discrimination performance one hour after stage 5 kindled convulsions were given to kindled rats. There was a significant main effect for STRAIN, where SLOW rats ($\bar{x} = 5.3$) performed significantly better overall than FAST rats ($\bar{x} = 4.8$), $F(1, 17) = 5.4$, $p < .05$. There was also a main effect for GROUP where the control animals ($\bar{x} = 5.3$) performed better than kindled animals ($\bar{x} = 4.8$), $F(1, 17) = 5.6$, $p < .05$. In addition, there was also a significant strain X group interaction $F(1, 17) = 7.3$, $p < .05$. As can be seen in Figure 10, the interaction was due to the much lower performance of the kindle FAST rats ($\bar{x} = 2.8$) compared to control FAST rats ($\bar{x} = 4.6$), $F(1, 6) = 72.1$, $p < .0001$, and compared to the kindled SLOWs ($\bar{x} = 5.3$), $F(1, 10) = 10.84$, $p = .008$. It is clear from the aforementioned results that the kindled rats continued to perform poorly.

Ten Minute Testing

Figure 11 shows the choice run arm discrimination performance 10 minutes after stage 5 kindled convulsions were delivered to kindled FAST and SLOW rats for

Figure 10. Mean ($\pm$ S.E.M.) correct arm discrimination choices for six trials. A stage-5 kindled convulsion preceded maze testing by 1 hour for each rat over 4 consecutive days.

each of 4 consecutive days. There was a significant main effect for strain where SLOW rats ($\bar{x} = 5.4$) performed superior to FAST rats ($\bar{x} = 3.6$), $F(1, 17) = 106.4$, $p < .0001$. This was due to the better performance of the kindled SLOWs ($\bar{x} = 5.5$) compared to the kindled FASTs ($\bar{x} = 2.8$), $F(1,8) = 77.4$, $p < .0001$, as well as the better performance of the SLOW controls ($\bar{x} = 5.39$) to the FAST controls ($\bar{x} = 4.6$), $F(1, 9) = 24.15$, $p = .001$. There was also a main effect for group where control animals ($\bar{x} = 5.1$) were superior to kindled animals ($\bar{x} = 4.4$), $F(1, 17) = 24.2$, $p < .001$ and a significant strain by group interaction $F(1, 17) = 30.1$, $p < .001$.

It can be seen in Figure 11 that the interaction was due to the poor performance of the FAST kindled group compared to all other groups, as confirmed by simple effects tests that showed the kindled FAST rats ($\bar{x} = 2.8$) were much lower in performance than the control FASTs ($\bar{x} = 4.6$), $F(1, 6) = 72.1$ $p = .0001$, and the kindled SLOWs ($\bar{x} = 5.5$), $F(1, 8) = 34.8$ $p < .001$. Thus the post-ictal period significantly and negatively impacted on the FAST compared to the SLOW strain.

Phase IV: Post-kindle Testing

Minute 1 Delay

After the completion of the post-ictal depression testing phase, and a 10 day rest period, post-kindle testing took place. Figure 12 shows the data for a 1 minute delay between the information run and the choice run for 5 consecutive days. There was a significant overall effect for strain; SLOW rats ($\bar{x} = 5.1$) were superior at arm

Figure 11. Mean ($\pm$ S.E.M.) correct choices for six arm discrimination trials per day.

A stage-5 kindled convulsion preceded the daily session of trials by 10 minutes, for each kindled rat over 4 consecutive days.

Figure 12. Mean ($\pm$ S.E.M.) correct choices for six daily arm discrimination trials over five days following a 10 day rest period from Maze running and kindling. The intratrial delay (the delay between the information run and the choice run) was 1 minute duration.

discrimination than the FAST rats ($\bar{x} = 4.2$), $F(1, 17) = 16.3$, $p = .001$. Simple effects showed that the kindled SLOW rats ($\bar{x} = 5.5$) were superior to the kindled FAST rats ($\bar{x} = 4.1$) $F(1, 6) = 9.3$, $p = .02$ and the control SLOW ($\bar{x} = 4.8$) rats were superior to the control FAST rats ($\bar{x} = 4.2$), $F(1, 11) = 4.95$, $p = .05$. Although there was no overall main effect for group, the kindled SLOW rats ($\bar{x} = 5.5$) performed better than the control SLOW rats ($\bar{x} = 4.8$), $F(1, 8) = 6.1$, $p = .03$. This surprising finding suggests that the retention for arm discrimination was better for the kindled SLOWs than the control SLOWs with a 1 minute delay.

Two Minute Delay

After a 2 day rest, the rats were tested at a 2 minute delay for 5 days. Figure 13 shows correct choices made for the choice run arm discrimination. There was a significant main effect for strain; SLOW rats ($\bar{x} = 4.4$) again did better than the FAST rats ($\bar{x} = 3.8$), $F(1, 17) = 4.9$, $p = .05$. Interestingly, the kindled SLOWs again performed better than the control SLOWs but the difference was not significant at the 2 minute delay.

Three Minute Delay

Following another 2 day rest, the rats were tested at a 3 minute delay for 5 days. Overall arm discrimination performance (Figure 14) again was shown to be superior in SLOW rats ($\bar{x} = 4.5$) compared to FAST rats ($\bar{x} = 3.5$), $F(1, 17) = 35.5$, $p = .0001$. There was also a significant strain X group interaction $F(1, 17) = 4.4$, p

Figure 13. Mean ($\pm$ S.E.M.) correct choices for six daily arm discrimination trials over five consecutive days. Formerly kindled animals were not rekindled during these trials. The intratrial delay was 2 minutes.

Figure 14. Mean ($\pm$ S.E.M.) correct choices for 6 daily arm discrimination trials over 5 consecutive days during which formerly kindled animals were not rekindled. The intratrial delay was 3 minutes.

=.05. Simple effects revealed that the interaction was because the control SLOW ($\bar{x}$ = 4.6) outperformed the control FAST ($\bar{x}$ = 3.4), $F(1, 7) = 54.2$, $p = .0001$, but the Kindled SLOW were not significantly different from the kindled FAST rats. One can see from Figure 14 that the kindled SLOW rats were becoming less proficient than previously, at the shorter time delays.

Five Minute Delay

After 2 more days rest, the rats were tested at a 5 minute delay for five days. MANOVA analysis for arm discrimination (Figure 15) revealed overall that SLOW rats ($\bar{x}$ = 4.3) performed better than FAST rats ($\bar{x}$ = 3.4), $F(1, 17) = 29.1$, $p = .0001$ and that control rats ($\bar{x}$ = 4.1) did better than kindled rats ($\bar{x}$ = 3.6), $F(1, 17) = 7.8$, $p = .02$. Simple effects for group showed that kindled FAST ($\bar{x}$ = 2.9) rats did worse than control FAST rats ($\bar{x}$ = 3.7) $F(1, 10) = 24.5$, $p = .001$. The same pattern was not seen for the SLOW rats. Simple effects for strain showed that the kindled SLOW ($\bar{x}$ = 4.2) performed better than kindled FAST rats ($\bar{x}$ = 2.9, $F(1, 7) = 18.2$, $p = .004$. Also, the control SLOW ($\bar{x}$ = 4.4) did better than the control FAST rats ($\bar{x}$ = 3.7), $F(1, 10) = .01$.

In summary, the SLOW strain did better than the FAST strain during all delay intervals, and the negative effect of kindling for both strains became more obvious for both strains at higher intertrial delays.

Figure 15. Mean ($\pm$ S.E.M.) correct choices for six daily arm discrimination trials over five consecutive days during which formerly kindled animals were not rekindled. The intratrial delay was 5 minutes.

Latency Results

The speed of latency with which the rats negotiated the maze showed consistent strain differences throughout the experiment; although certain changes did occur in different experimental phases (see below). In general, however, the SLOW rats showed longer latencies than the FAST rats.

In phase 1, during acquisition of the maze, the SLOW rats were initially much slower in running the maze than the FAST rats. Within 5 days, however, both strains became far more similar for both the information run (Figure 16) and the choice run (Figure 17). However, differences still were often apparent between the strains, where the SLOW rats ran slower than the FAST rats. See Appendix B for detailed statistical assessment. In phase 2, when the kindling treatment was applied 23 hours before maze training, the small difference between SLOW and FAST rats from phase 1 was maintained. That is, the SLOW rats generally continued to run slower than the FAST rats, independent of kindling (Appendix B).

During phase 3, however, with the progressively shorter intervals between the convulsion and the maze task, a change in the running speed was noted. At this time the convulsion 1 hour earlier exerted its effect. This effect was differential between the strains. More specifically, the kindled FAST rats ran slower than their FAST controls, while the kindled SLOW rats ran faster than their SLOW controls. Thus 1 hour after a convulsion, SLOW rats experienced a behavioral increase involving mobility, in counterdistinction to the FAST rats. A similar pattern was also apparent

Figure 16. Mean ($\pm$ S.E.M.) information run latencies corresponding to the days of the stem discrimination learning trials in Figure 3. Each day is the mean time for 6 trials for each rat.

Figure 17. Mean ($\pm$ S.E.M.) choice run latencies corresponding to the 10 days of arm discrimination learning trials in Figure 6. Each day is the average of the six trials per group.

at the 10 minute post-ictal interval (see Appendix B for detailed results).

Lastly, during phase 4, when the convulsions were no longer triggered in the kindled rats, the SLOW rats returned to a profile of longer latencies relative to FAST rats, and no clear effect of kindling on either strain was seen (Appendix B).

Discussion

Pretreatment Memory Performance

From the beginning of the experiment, it was apparent that the strains had some similarities and several differences in the acquisition of T-maze tasks. Baseline learning rates for the reference memory tasks were essentially the same for the two strains. Clear differences showed in the working memory task where SLOWs acquired the task within half the time of the FASTs. Similar results were found in the radial arm maze between the strains (Smith, 1993). Also, the SLOWs, on average continued to outperform the FASTs throughout the remainder of the experiment.

The working memory differences between the SLOWs and FASTs may reflect strain differences in the anatomical neurochemistry of the limbic system areas that support working memory. Neurochemical analysis has shown that the SLOW strain has higher levels of olfactory or piriform cortex noradrenergic (NE) levels, higher medial amygdala and piriform serotonergic (5-HT) levels, and higher DOPAC levels in CA1 of the hippocampus than the FAST strain. Although this appears to be a considerable mosaic of neurochemistry differences, both NE and 5-HT are thought to be particularly important for learning and memory processes (Cai, 1989). The higher levels of these neurotransmitters in the SLOW strain might account for their better working memory performance compared to the FAST strain..

T-maze Latency and the Strains

Latency scores can be a measure of maze performance for inferring memory performance in paradigms such as the Morris water maze (Morris, 1983). However, in the T-maze, memory performance is inferred from correct choices, and latency scores are used as an indication of the level of motivation to run the maze. Once the T-maze task is well learned, hungry rats will typically have short latencies. Longer latencies combined with poor choice performance might indicate a lack of motivation to run, due to illness or because of an overfeeding error on the part of the experimenter. If this should occur, however, it usually does so infrequently and only to a single rat at a time. As such, the occurrence is easily identifiable as a lack of motivation for specific causes due to the singularity of its occurrence, and is easily corrected. However, in the present experiment, the entire SLOW strain had longer latencies than the FAST strain.

The latency scores for the 2 strains showed stable group differences that were maintained throughout the experiment. Ironically, the slower learning FAST strain was much faster at running the maze than was the SLOW strain. It should be clarified, however, that animals from both strains showed good motivation to run the maze, and the SLOW rats were probably not less motivated. More likely, the differences in latency scores between the strains in the present experiment were probably related to the behavioral observations from past experiments that showed the SLOW rats as

more fearful, more inhibited, less impulsive, and less ambulatory compared to the FAST strain (Mohapel, 1993).

Initial Kindling and Memory

From the first day of kindling, the memory performance of stimulated rats was compared to their respective controls. Daily kindling stimulations were accompanied with the development of ADs and the eventual expression of behavioral seizures. The latter ranged in severity from stage 1 to stage 5. From stage 1 to stage 2-3 seizure, kindled animals from both strains showed no group differences in performance compared to their control counterparts. The FAST rats as a group showed a significantly more rapid increase in the AD duration than the SLOW rats (Figure 2). Despite the more rapid AD increase, however, the stimulated FAST rats still displayed no reference or working memory impairments compared to the FAST control rats. Therefore, the initial stages of kindling, those associated with shorter AD lengths and less evolved behavioral seizures, did not appear to seriously affect memory performance. As such, the early stages of kindling epileptogenesis, could only be associated with mild functional impairments that do not significantly affect working or reference memory in the T-maze. This result is consistent with other recent studies that have found no memory impairments in rats during partial limbic kindling (Robinson, McNeill, & Reid, 1993; McNamara et al., 1993).

Effects of Stage 5 Seizures on Memory

The development of generalized stage 5 seizures were shown to affect the strains differently than the milder partial seizures. The working and reference memory performance of the SLOW rats was largely unaffected by the induction of stage 5 seizures delivered 23 hours prior to maze performance. Indeed, the kindled SLOWs actually outperformed the controls on many days, although the difference was not significant. Conversely, the working memory performance of the FAST strain was readily disrupted by the previously delivered stage 5 seizure.

The time interval between the seizure and memory testing was critical for determining whether decrements in performance are due to immediate postictal effects, or effects of the kindling *per se*. The presence of a memory impairment in the FAST rats 23 hours after a stage 5 ictal event was unique as impairments so long after a seizure are rarely demonstrated in other studies. It suggested that the memory impairment might be due to relatively permanent brain changes associated with generalized seizures. Such chronic brain changes should affect memory independent of immediate post-ictal effects, and could otherwise be thought of as functional lesions. These changes were only conspicuous in the FAST rats.

It should be mentioned, however, that the memory performance of the FAST strain did not remain low permanently, and began to recover with time, even though they continued to receive stage 5 seizures after full kindling. It is not known precisely

why this occurred. One possibility is that fully generalized seizures may initially induce a protracted post-ictal state that is associated with an altered cognitive state in the FAST rats. This protracted state might then render the rats temporarily amnesic for past learning that occurred in the non-seizured state. If such a protracted state-dependent learning could occur, then the FAST rats would reacquire the maze task in the new post-kindled state, and show a new learning curve (albeit a short one). State dependent learning is a well recognized phenomenon in the psychological literature, and has been shown to occur in rats between the normal, ictal and post-ictal state (McIntyre & Reichert, 1970; McIntyre & Gunter, 1978; McIntyre, Stenstrom, Taylor, Stokes, & Edson, 1984).

Post-Ictal Depression and Memory

Post-ictal depression refers to a state of confusion, disorientation, prograde or anterograde amnesia and general cognitive impairment immediately after an ictal or convulsive event. (Pincus & Tucker, 1978). It induces an acute cognitive impairment that lasts for varied lengths of time and frequently presents in EEG recordings as abnormal background activity. The duration of the post-ictal depression is one way of measuring the cognitive impact of the seizure episode on the organism.

At 1 hour post-ictus, the working memory performance of the SLOW strain was unaffected by the earlier stage 5 seizures compared to controls. On the other

hand, the working memory of the FAST strain, however, was significantly impaired compared to FAST controls. Therefore, the SLOWs readily showed the ability to recover working memory functions within 1 hour of an ictal attack whereas the FAST strain were not. Similarly, in a different laboratory, memory impairments were demonstrated after kindled stage 5 seizures that were electrically induced 25-45 minutes before reversal learning in the Morris water maze (McNamara, 1993).

Remarkably, at 10 minutes post-ictus, the kindled SLOW rats continued to show levels of working and reference memory performance that were unaffected compared to their control counterparts. As before, the FAST strain showed significant working memory impairments at 10 minutes post-ictus compared to their controls. In addition, at this time interval, there was also a significant reference memory impairment in the kindled FAST rats compared to both the control FAST as well as the kindled SLOW rats. Since reference memories are thought to be permanent and resistant to disruption (Olton, Becker & Handleman, 1979), this result is an indication that antecedent seizures can more extensively disrupt memory in a more excitable nervous system like that seen in the FAST strain.

Since reference memory is impaired in rats (Stokes & Best, 1988; 1990) and humans (Victor, Adams, Collins, 1971; Speedie & Heilman, 1983; Squire & Moore, 1979; Squire, 1988) with mediodorsal thalamic lesions, possibly the functional integrity of these thalamic structures was compromised in the FAST rats by the generalized seizure 10 minutes earlier. This suggests that the propagation of epileptiform activity is furthermore extensive anatomically in the FAST than the

SLOW strain, and/or induces a more protracted disruption of normal function in these other structures.

Electrophysiological Measures and Memory

Electrophysiological assessment of the females in the SLOW and FAST strains confirmed that they have maintained their respective rates of kindling compared to the males when they were last examined (Dufresne, 1990; Mohapel, 1993). The triggered excitability in the amygdala of the SLOW rats was much reduced compared to that of that of the FAST rats. This was measured both in the duration of the local AD, and the rate at which this AD propagated to trigger fully kindled seizures.

It was surprising to find no significant differences in AD duration, convulsion length, convulsion latency between the fully kindled rats of the 2 strains. It is intuitively easy to see that, for example, longer AD durations in the FAST rats could contribute to their greater memory impairment compared to SLOW rats that tended to have shorter AD durations. This perspective is consistent with one finding (McNamara et al., 1993) that the AD of stage 5 kindled seizures is responsible for memory disruption when the seizure is elicited moments prior to or after maze performance. This seemed likely because fully kindled SLOW rats typically have shorter afterdischarges from amygdala kindling compared to the fully kindled FAST rats (Dufresne, 1990; Mohapel, 1993). In the present study, the SLOW strain had

shorter afterdischarges than the FAST strain, but this difference was not significant except for the first 17 days of kindling (Figure 2) when there was no difference between the memory of kindled and control animals in both strains. Also, there was no significant difference in AD duration when all the rats from both strains have been fully kindled, despite working memory impairments for kindled FAST but not kindled SLOW rats. It should be noted, however, that the AD duration of the SLOW rats tended to be shorter than those of the FAST rats, even though the difference was not significant. This implies that longer AD durations may be contributing to memory impairment in the presence of some other factor(s) (i.e., genetic, biochemical, neuroanatomical), but full kindling in itself does not impair memory, otherwise the memory performance of the SLOW strain would have been impaired once full kindling had been established.

Post-Stimulation Maze Tests

Daily memory testing after a 10 day rest period was resumed to determine whether any long term effects of kindling *per se* were detectable in previously kindled rats. On retesting at a 1 minute delay, the kindled FAST rats were shown to be similar to the control FAST rats. This was an interesting finding when one considers the conspicuous impact kindled seizures had on the FAST rats in previous testing phases of the experiment. It should be noted, however, that working memory

performance of the kindled and control FAST was below criterion levels and significantly lower than that of the SLOW strain. Therefore, the overall lower retention for the working memory task by the FASTs was to a large degree a function of strain and less so due to kindling.

It was a surprise to discover that the kindled SLOW rats performed better for the first six days of retesting than the controls. There are no studies showing that kindling improves memory. One possible explanation may come from a finding where kindling affected a fear response but did not affect memory (Nieminen, 1992). If the kindled SLOWs were moderately less fearfully than the controls, it may manifest as better performance in the T-maze task (or vice versa).

When task difficulty was changed to a 2 minute intertrial delay, only the basic strain differences were apparent, and the performance of kindled animals was no different from their control counterparts for each strain. Interestingly, the kindled SLOWs continued to perform slightly better than the control SLOWs but the difference was no longer significant.

At a 3 minute intratrial interval, the SLOW rats again were superior to the FAST rats. However, this was due to the superior working memory performance of the SLOW controls compared to the FAST controls. There was no difference in maze performance between kindled SLOW and kindled FAST rats. This was also the first instance where the control SLOWs consistently outperformed the kindled SLOWs. As such, kindled SLOW animals were beginning to show a working memory impairment compared to their controls, even though the difference was not statistically significant.

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At a 5 minute intertrial interval, however, the effects of kindling on memory were even more apparent. As expected the SLOW strain in general outperformed the FAST strain on working memory performance. In addition, the kindled FAST animals now performed significantly worse than the FAST control animals. Although the kindled SLOW rats did worse than the control SLOW, the difference fell short of significance.

The overall result showed that control animals from both strains significantly outperformed their kindled counterparts. Since the kindled animals had been unstimulated for several weeks by the end of the experiment, the lower memory performance of the kindled group at the 5 minute intertrail interval was likely the result of functional lesions affecting limbic structures involved in working memory. Note that the functional memory impairment in kindled animals was detected only at the most challenging level (5 minute delay) of maze testing. Increasing the task difficulty is not routinely done on tests of memory in animal studies, which is probably one source of null results when looking at the effects of kindling *per se* on memory.

Overall Memory Profile of the Strains

The SLOW strain demonstrated resistance to kindling epileptogenesis, requiring many more kindling stimulations to full convulsive kindling, and having somewhat shorter afterdischarges and seizure durations and shorter recovery periods from post-

ictal depression. When left unstimulated for 10 days, only mild cognitive impairments were detected at the highest difficulty levels of the T-maze task. On the other hand, the FAST strain demonstrated a much greater susceptibility to kindling epileptogenesis, requiring fewer stimulations to full kindling, having longer AD and seizure durations, and longer intervals of post-ictal depression. When left unstimulated for a period of time, cognitive impairments were conspicuous compared to control animals of the same strain..

It is probably not a coincidence, however, that the SLOWs have superior baseline working memory performance as well as resistance to epileptogenesis. One explanation for the association of resistance to epilepsy and better memory might be due to the integrity of central noradrenergic receptors. It is known that the depletion of noradrenaline facilitates kindling (Arnold, Racine & Wise, 1973; McIntyre, Saari & Pappas, 1979; McIntyre, 1980). In addition, noradrenergic agonists retard kindling (Gellman et al., 1987; McIntyre & Guigno, 1988; Pelletier & Corcoran, 1993). Noradrenergic systems are also involved in memory modulation in the amygdala (Liang et al., 1986; 1990; Cai, 1986; McGaugh et al., 1990; McGaugh et al., 1993). Recently, the beta-adrenergic receptors have been found to be more critical for memory functions (McGaugh et al., 1993). In the amygdala, beta-noradrenergic receptors modulate memory by activating the release of acetylcholine (Dalmaz, 1993).

Genetic differences likely account for differences in the levels of central norepinephrine(NE). It is known that the SLOW strain has higher levels of limbic norepinephrine compared to the FAST strain (Dufresne, 1990). As such higher levels

of NE (a) would tend to retard kindling at the post-synaptic receptor and (b) would be needed to ensure adequate memory function at the level of the beta-adrenergic receptors. Lower NE levels in the FAST strain would account for the effects of lower baseline memory performance and kindling susceptibility. The particularly adverse effects of kindling on memory functions in the FAST strain may be due to additional depletion of already low levels of NE that exist in the strain. The effect of kindling would be particularly detrimental to the memory of the FAST strain because kindling has been shown to deplete NE and reduce the beta-adrenergic receptors (McIntyre & Roberts, 1983). Since it is the beta receptors that are most involved in memory, a further selective depletion of NE and beta adrenergic receptors in an animal that is already genetically lower in NE is likely to show a more pronounced memory impairment. Therefore, in light of this evidence, NE possibly plays a key role in the way kindling epileptogenesis affects memory.

Summary

The data from the present experiment provides evidence that genetic factors influence the impact of kindling and kindled seizure perturbation on memory. A greater resistance to epilepsy in this instance appears to be accompanied by faster learning and a memory that is relatively more resistant to perturbation. This might be due to properties in the neurobiochemical or anatomical substrate that is shared by

both epilepsy and memory phenomena. Genetic animal models of epilepsy can provide insight for understanding the mechanisms that govern the interaction of normal processes such as memory with abnormal ones like epilepsy. Memory research continues to benefit from a study of the epilepsies.

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Appendix A

Reference Memory Results

Phase III Part 1: One Hour Post-ictal Depression Testing

Figure 4 shows stem discrimination for part 1 of phase III. The performance of the SLOW strain ($\bar{x} = 5.9$) was significantly more accurate than the FAST strain ($\bar{x} = 5.6$), $F(1, 6) = 4.5$, $p = .05$. The control SLOW ($\bar{x} = 6.0$) performed better than the kindled SLOW ($\bar{x} = 5.8$), $F(1, 6) = 8.4$, $p > .02$. Compared to the control SLOW ($\bar{x} = 6.0$) the performance of the kindled SLOW also decreased over time, as indicated by a significant within groups factor for group (kindled versus control by days $F(3, 18) = 6.0$, $p = .005$. It should be mentioned that the difference between the control and kindled SLOW rats is in reality a small one, probably due to a ceiling effect for the control SLOW rats which was not observed for the kindled SLOW rats.

Phase III Part 2: 10 minute Post-ictal Depression Testing

Figure 5 shows stem discrimination performance 10 minutes after stage 5 kindle convulsions in SLOW and FAST rats. There was a significant main effect for strain where SLOW rats ($\bar{x} = 5.9$) outperformed the FAST rats ($\bar{x} = 5.3$), $F(1, 17) = 19.2$, $p < .001$. and for group; control rats ($\bar{x} = 5.9$) outperformed kindled rats ($\bar{x} = 5.50$), $F(1, 17) = 14.0$, $p < .01$. There was a significant strain by group interaction $F(1, 17) = 20.4$, $p < .001$, which was due to the lower overall performance of the

kindled FAST rats ($\bar{x} = 4.8$) compared to control FASTs ($\bar{x} = 5.8$), $F(1, 6) = 15.8$, $p < .01$, and the kindled SLOWs ($\bar{x} = 5.9$), $F(1, 8) = 34.8$, $p < .001$. The within subjects factors analysis showed a significant group by days interaction $F(3, 51) = 3.4$, $p = .02$, which was due to the decrease in performance of the kindled FAST rats compared to the control FAST rats $F(3, 24) = 6.0$, $p = .005$. There was also a group by strain by days interaction $F(3, 61) = 5.6$, $p = .002$, which was due to the decrease in performance of the kindled FASTs compared to the kindled SLOWs $F(3, 18) = 8.2$, $p = .001$.

Appendix B

Latency Scores

Phase I: Initial Acquisition

Overall latency scores for the first 9 days of the choice run (Figure 16) showed that the SLOW rats ($\bar{x} = 52.6$) had much longer running times than FAST rats ($\bar{x} = 19.1$), $F(1, 20) = 18.8$, $p = .0001$, however, they soon caught up to the FAST rats, as indicated by a significant within subjects effect for days $F(8, 160) = 17.5$, $p = .0001$, with a significant strain X days interaction $F(8, 160) = 7.8$, $p < .001$.

The latency for the information run (Figure 17) was much like the choice run and shows that the SLOWs ($\bar{x} = 73.1$) took longer to run than the FAST rats ($\bar{x} = 24.8$), $F(1, 20) = 18.3$, $p < .001$. Again, however, the SLOWs improved their running time to parity with the FAST rats as confirmed by a significant DAYS effect $F(8, 160) = 28.0$, $p < .0001$ with a significant STRAIN x DAYS interaction $F(8, 160) = 13.3$, $p < .001$.

Phase II: Kindling Trials

Figure 18 shows latencies for the choice run that corresponds to the arm discrimination task of the last 6 days of kindling in Figure 9. There was a main effect for strain, where the SLOW rats ($\bar{x} = 13.0$) took significantly longer to run the maze than FAST rats ($\bar{x} = 8.0$), $F(1, 17) = 7.3$, $p = .015$.

MANOVA analysis of information run latencies (Figure 19) showed that the SLOW rats ($\bar{x} = 16.6$) also took significantly longer to complete stem discrimination on the information run of the maze trials than the FAST rats ($\bar{x} = 10.9$), $F = 5.5$, $p < .03$. Simple effects showed no difference between kindled SLOW and kindled FAST. The difference was due to the slower running of control SLOWs ($\bar{x} = 11.5$) to the control FASTs ($\bar{x} = 7.6$), $F(1, 9) = 6.0$, $p < 0.03$. This was despite the fact that there was no significant difference for correct stem choices between SLOW and FAST rats in the stem discrimination task. It appears that the differences arise from the very long latencies ($\bar{x} = 50$) of the SLOW control group for day three. Since the control SLOWs do not show high latency scores for the other three days, this result is probably artifactual and not related to the experimental treatments.

Phase III Part 1: 1 Hour Post-ictal Depression Latencies

The choice run latencies for arm discrimination 1 hour after a stage 5 convulsion (Figure 20) show a significant strain by group interaction $F(1, 17) = 6.2$, $p < 0.05$. Simple effects showed that the FAST control rats ($\bar{x} = 11.1$) ran faster than the FAST kindled rats ($\bar{x} = 17.9$), $F(1, 6) = 5.8$, $p = .05$. However, the opposite was apparent for the SLOWs, where the kindled SLOWs ($\bar{x} = 10.7$) ran faster than the

Figure 18. Mean ($\pm$ S.E.M.) choice run latencies for T-Maze performance preceded 23 hours by stage-5 kindled convulsions over the last six days of kindling.

Figure 19. Mean ($\pm$ S.E.M.) information run latencies for six daily trials on the final six kindling days. Kindled rats experience stage-5 kindled convulsions 23 hours prior to each daily session of trials over 4 consecutive days.

Figure 20. Mean ($\pm$ S.E.M.) choice run latencies for six daily trials of T-Maze performance. The daily session of trials was preceded 1 hour by a stage-5 kindled convulsion for each rat over the 4 consecutive test days.

control SLOWs ($\bar{x} = 15.6$) = 5.2, $p > .05$. Thus, at 1 hour, convulsions facilitated the SLOW rats' mobility but depressed the mobility of the FAST rats.

Phase III Part 2

10 Minute Post-ictal Depression Testing

A similar pattern was apparent in the 10 minute post-ictal manipulation. Figure 21 shows the latencies for the choice run trials 10 minutes after a stage 5 convulsion. There was a significant strain X group interaction $F(1, 17) = 11.0$, $p < .01$. Again the simple effects showed that the kindled FASTs ($\bar{x} = 17.9$) were much slower on the choice run than the control FASTs ($\bar{x} = 11.1$), $F(1, 6) = 5.8$, $p = .05$, or the kindled SLOWs ($\bar{x} = 10.7$), $F(1, 8) = 21.1$, $p = .002$, while the kindled SLOW rats were faster ($\bar{x} = 10.7$) than the SLOW control rats ($\bar{x} = 15.6$), $F(1, 11) = 5.22$, $p > .05$. This same result between kindled and control SLOWs was also seen at 1 hour post ictus for the stem discrimination.

Phase IV: Post-kindle Testing at 3 Minute Delay

When convulsive seizures were absent, a different pattern of latencies occurred at longer delays. MANOVA analysis of Latency scores (Figure 22) for the choice run

Figure 21. Mean ($\pm$ S.E.M.) choice run latencies for six daily trials of T-Maze performance. The daily session of trials was preceded 10 minutes by a stage-5 kindled convulsion for each rat over the 4 consecutive test days.

Figure 22. Mean ($\pm$ S.E.M.) choice run latencies for six daily arm discrimination trials over five consecutive days during which formerly kindled animals were not rekindled. The intratrial delay was 3 minutes.

in for showed a main effect for strain; SLOW rats ($\bar{x} = 17.5$) took longer to run than FAST rats ($\bar{x} = 7.7$), $F(1, 17) = 10.3$, $p = .005$. Simple effects showed that the kindled SLOW ($\bar{x} = 12.4$) took longer than the kindled FAST ($\bar{x} = 7.6$), $F(1, 17) = 20.2$, $p = .003$ and the control SLOW ($\bar{x} = 21.7$) took longer than the control FAST ($\bar{x} = 7.7$) $F(1, 17) = 7.96$ $p = .02$.

MANOVA analysis of information run Latencies for 3 minute delay (Figure 23) showed an overall strain effect; SLOW rats ($\bar{x} = 24.2$) took longer than FAST rats ($\bar{x} = 12.4$), $F(1, 17) = 8.5$, $p = .01$. Simple effects revealed that the main effect was due to the slower running of control SLOWs ($\bar{x} = 29.4$) compared to the control FAST ($\bar{x} = 12.3$), $F(1, 10) = 7.3$, $p > .03$. Also, the within-subjects factor analysis revealed a significant strain X days interaction $F(4, 68) = 2.9$, $p > .03$. The running time for the SLOW rats decreased over days (Figure 21) to that of control FAST rats which slightly increased by day five $F(4, 40) = 4.0$, $p > .01$.

Post-kindle Testing at 5 Minute Delay

Choice run Latencies are illustrated in Figure 24. MANOVA analysis showed overall that SLOW rats ($\bar{x} = 14.6$) took longer than FAST rats ($\bar{x} = 7.9$), $F(1, 17) = 16.9$, $p = .001$. Simple effects tests revealed this to be due slower running of the kindled SLOW ($\bar{x} = 11.8$) compared to the kindle FAST ($\bar{x} = 7.3$), $F(1, 7) = 29.7$, $p = .001$ and the slower running of the control SLOW ($\bar{x} = 16.9$) to the control FAST ($\bar{x} = 8.3$), $F(1, 10) = 10.5$, $p = .009$. Differences in latencies for the information run (Figure 25) were also present. MANOVA showed overall that the SLOW rats ($\bar{x} =$

Figure 23. Mean ($\pm$ S.E.M.) information run latencies for six daily arm discrimination trials over five consecutive days during which formerly kindled animals were not rekindled. The intratrial delay was 3 minutes.

Figure 24. Mean ($\pm$ S.E.M.) choice run latencies for six daily arm discrimination trials over five consecutive days during which formerly kindled animals were not rekindled. The intratrial delay was 5 minutes.

Figure 25. Mean ($\pm$ S.E.M.) information run latencies for six daily stem discrimination trials over five consecutive days during which formerly kindled animals were not rekindled. The intratrial delay was 5 minutes.

20.3) were slower than FAST rats ($\bar{x} = 11.2$), $F(1, 17) = 8.8$, $p = .009$. Simple effects revealed that the control SLOW ($\bar{x} = 23.2$) ran slower than the control FAST ($\bar{x} = 10.7$), $F(1, 10) = 7.4$, $p = .021$, but there were no differences between kindled SLOW and kindled FAST rats.

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