The Impact of Neonatal Seizures on the Ability to Encode, Store, and Retrieve Memories

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Throughout life, the prevalence of seizures is highest during the neonatal period, a critical time for synaptic development. While neonatal seizures can be attributed to a wide array of predisposed risk factors and underlying medical complications, the majority of seizures result from hypoxic-ischemic encephalopathy, a condition that occurs when the brain is deprived of adequate oxygen supply. Early life neonatal seizures often result in cognitive deficits such as long-term impairments in learning and memory. Additionally, the occurrence of seizure activity during the this developmental period increases susceptibility to epilepsy far into adulthood. In this study, we propose two distinct sets of hypotheses to explain the origin of cognitive dysfunction resulting from neonatal seizures. From a psychological perspective, the extensive and far-reaching effects of such seizures can be rationalized using components from existing memory models. Furthermore, these deficits can be explained on a synaptic level through the physiological association between long-term potentiation and the ability to encode, store, and retrieve memories.
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INTRODUCTION

Neonatal seizures, which can be attributed to a variety of etiologies, occur in 1.8 to 3.5 per 1,000 live births (Cowan, 2002; Cowan et al., 2003; Silverstein & Jensen, 2007). Throughout life, the prevalence of seizures is highest during the neonatal period, a critical time for both psychological and physiological development. Neurological disruption during this period often has detrimental and far-reaching effects on the cognitive function of affected infants. They are a problem in both term and pre-term infants and are secondary to risk factors such as shortened gestational period, low birth weight, and male sex (Kohelet, Shochat, Lusky, & Reichman, 2006a; Kohelet, Shochat, Lusky, & Reichman 2006b; Kurabe, Sorimachi, Sasaki, Koike, & Fujii, 2009). Additionally, these seizures can be associated with a host of underlying conditions, such as transient metabolic disturbance, systemic or central nervous system infection, cerebrovascular abnormalities, and hypoxic-ischemic encephalopathy (Hallberg & Blennow, 2013). While an array of factors contributes to the onset of neonatal seizures, neonatal encephalopathy due to hypoxia-ischemia is the most common cause of seizures in neonates (Hallberg & Blennow, 2013; Silverstein & Jensen, 2007). During hypoxic-ischemic encephalopathy (HIE), brain injury to both gray and white matter structures often occurs as a result of asphyxia, most specifically, damage to the basal ganglia and thalamus (Gano et al., 2013).

Unlike seizures that occur during adulthood, neonatal seizures are difficult to detect and treat because they are most commonly associated with subtle behavior and a lack of coordinated EEG pattern (Jensen, 2009). Given the range of variability in neonatal seizures, it is important to distinguish the difference between these seizures and
general epilepsy. Epilepsy in children includes a body of disorders that is characterized by recurrent, unprovoked seizure activity. Neonatal seizures, while not considered an epileptic disorder, are a specific type of seizure that occur within the first 28 days of life and often contribute to the future development of epilepsy. In addition, febrile seizures, congenital malformations, metabolic disorders, head trauma, CNS infection, and family history are specific risk factors that are indicative of epilepsy later in life (Cowan, 2002). Interestingly, many of these risk factors for epilepsy independently contribute to the onset of neonatal seizures. To fully understand how seizures affect memory, the pathology of these seizures must first be understood.

The clinical expression of neonatal seizures often inhibits a clear diagnosis, as both inward and outward symptoms tend to vary greatly depending on the etiology and type of seizure. A review by Silverstein and Jensen (2007) detailing the clinical and electrical differences in the types of seizures seen in neonates suggests that each of these factors is associated with a specific outcome. Subtle seizures, which account for approximately 50% of all neonatal seizures, are characterized by motions that imitate normal behaviors in neonates and are not consistently associated with EEG seizure activity. Tonic seizures, when focal, exhibit sustained muscle contractions and coordinated EEG activity. Similarly, focal clonic seizures display evident EEG seizure activity, but are outwardly associated with rhythmic jerks. Finally, myoclonic seizures are characterized by rapid, single, arrhythmic jerks. Though the initial diagnosis is often based on clinical observation, EEG seizure activity is the most definitive indicator of short-term outcome. Since neonatal seizures commonly have a debilitating effect on
quality of life, early diagnosis using these indicators are critical in managing and minimizing the risk to long-term cognitive function (Silverstein & Jensen, 2007).

Unfortunately, the spectrum of disorders that provoke the onset of neonatal seizures is simply too broad for the scope of this study. For this reason, our analysis of the effects of neonatal seizures on memory deficits will be limited to those resulting from hypoxic-ischemic encephalopathy, the most prevalent cause of neonatal seizures. In an effort to understand both the psychological and physiological impact of these seizures and assess how cognition is affected, a thorough analysis of the neonatal stage of development will be performed. The intent of this paper is to integrate a working knowledge of memory formation with a physiological understanding of neonatal seizures to fully explain how these seizures affect cognitive functioning. In doing this, we will present two sets of original hypotheses: one set that relates the cognitive deficits from neonatal seizures to existing memory models and another that explains the connection between the neural substrates of memory and the neural substrates of seizures. We will first discuss what is known regarding the cognitive deficits associated with neonatal seizures, specifically those associated with learning and memory. To explain these deficits from a psychological perspective, we will examine both early and revised models that have been proposed to explain the process of memory formation. Following this, we will explore the neural basis of memory formation and relate it to the molecular processes that occur during seizures.
COGNITIVE EFFECTS OF NEONATAL SEIZURES

Long-Term Complications

The risk for seizures is highest in the neonatal period, a critical period for both psychological and physiological development (Jensen, 2009). Seizures during this period are predominantly caused by HIE, a pathology that contributes to motor and cognitive deficits in up to 40% of surviving neonates (Silverstein & Jensen, 2007; Shankaran 2009). MRI findings indicate that the extent and severity of brain injury is commonly associated with the duration of the seizure (Glass et al., 2009; van Rooij, van den Broek, Rademaker, & de Vries, 2013).

The adverse outcomes associated with seizures resulting from HIE are most severe in the absence of other disabilities, such as cerebral palsy. For instance, a “normal” child is more likely to experience severe adverse outcomes from HIE-induced neonatal seizures than a child who has already been diagnosed with a cognitive disorder. These outcomes include intellectual impairments, memory and verbal problems, difficulty in executive functions, and motor problems (Perez et al., 2013). Issues with short-term memory and social interaction often extend far past childhood and into the adult years (Lindstrom et al., 2008; Odd, Dunnell, Lewis, & Rasmussen 2011). A study by van Handel, de Sonneville, de Vries, Jongmans, and Swaab (2012) found that seizures from moderate HIE result in the compromised maintenance and retrieval of verbal, visuospatial, and associative memories, while also decreasing the speed and efficiency of working memory. In cases resulting from only mild HIE, patients showed normal short-term and working memory with only a slightly weakened verbal learning capacity. Additionally, neonatal HIE can contribute to later-life developmental amnesia.
Developmental amnesia is a selective disorder characterized by a patient’s frequent failure to remember events from their everyday life. In these cases, deficits are observed in episodic memory while the function of semantic memory and working memory remain largely intact (Sans, 2011).

Methods of Treatment

In neonates that exhibit pharmacoreistant seizures, epileptic surgeries have been effective in reducing the severity of cognitive deficits. Two and ten-year follow up studies show improvement in social conduct, verbal learning capacity, figurative learning capacity, and working memory (Viggedal, Kristjansdottir, Olsson, Rydenhag, & Uvebrant, 2012). Interestingly, these patients exhibited signs of memory reorganization both prior to and immediately following the procedure (Viggedal et al., 2012). Because seizure disorders cause an inability to properly form memories, the brain attempts to preemptively compensate for the lack of function by reorganizing the process for memory consolidation. For instance, the posterior remnant of the hippocampus ipsilateral to the damaged hemisphere appeared to take over the function of verbal memory after the resection of an affected anterior temporal lobe (Bonelli et al., 2013). Despite the evident success with surgical intervention for recurrent seizures, recent advances have employed the use of therapeutic hypothermia to noninvasively treat and prevent future seizures (Harbert et al., 2011). Clinical trials indicate that post-seizure hypothermia reduces the extent of brain injury contributing to social dysfunction and impaired memory by preventing the molecular cascade that leads to secondary energy failure and eventual cell death (Dehaes et al., 2013).
Etiology of Cognitive Dysfunction

In understanding the foundation of developmental impairments from neonatal seizures, as well as the success of treatment methods, we can begin to hypothesize precisely how memory is affected. Memory is a complex concept that depends widely upon the type of information to be stored and the current stage of processing in which it resides. It is unknown whether seizure activity affects the capability to encode, store, or retrieve information that is intended for memory.

Three separate models, as detailed in Figure 1, have been suggested as possible explanations for reduced cognitive functioning in infants exhibiting seizure activity (Martinos et al., 2012). The first explanation proposes that neonatal seizures themselves directly cause the brain damage responsible for cognitive deficits. The second model suggests that the relative risk factors that predispose neonates to seizures, such as gestational length, birth weight and sex, act independently from seizures to hinder cognition and contribute to memory deficits. The third possible explanation integrates the first two models by suggesting that the overarching effect of a predisposition to brain injury along with actual seizure activity causes the severe memory impairments commonly seen in affected patients.

Figure 1. Models proposed by Martinos et al. (2012) to explain the relationship between neonatal seizures and memory deficits
MEMORY PROCESSES

Multi-Store Memory Model

As a topic of long-time psychological interest, various abstract models have been proposed to provide representations of how memory is believed to work. One of the earliest models for memory, the multi-store model proposed by Atkinson and Shiffrin (1968), divided memory into short-term and long-term components (Figure 2). Unlike other theories of the time, the multi-store model supported the idea of a dichotomized memory. Early studies demonstrated that patients with hippocampal lesions retained both their previous long-term memories and the ability to create new short-term memories (Milner, 1959; Milner, 1967). However, they lacked the ability to move these new short-term memories into long-term storage (LTS), thus supporting the notion that there is a distinct separation between short-term storage (STS) and LTS.

The multi-store model proposed that sensory stimuli are immediately registered and used to create trace memories. Memory traces may vary in strength depending on the
intensity of their associated meanings, a property that later affects the success of retrieval. Unless these traces are committed to STS, and ultimately LTS, they will quickly decay. Recent studies have noted that there is a maximum capacity, or buffer, for sensory information during the initial encoding process. Often, the failure to filter input within this buffer contributes to the loss of information from STS, rather than a failure of memory consolidation itself (Buschman, Siegel, Roy, & Miller, 2011). Though other forms of STS exist, Atkinson and Shiffrin relied heavily on auditory-verbal-linguistic (AVL) short-term store to explain their model. AVL, most widely studied by Peterson and Peterson (1959), demonstrated that stimuli that appeal to either the sense of sight or sound could be registered by the other sense before being transferred to STS for coding. They suggested that both task difficulty and the rate at which information is presented directly decreases available rehearsal time, which causes a decay of STS and ultimately affects the ability to accurately recall information. If coding is interrupted by additional tasks or stimuli, the transfer is terminated and the memory trace, along with its associated meaning, will decay before reaching STS.

The transfer of traces from STS to LTS is regulated by a variety of control processes, which will be discussed shortly. However, it is important to note that this transfer could be either probabilistic or continuous in manner depending upon the type of stimuli and the order in which they are presented. Probabilistic transfer occurs in cases of incidental learning where the subject does not make a conscious effort to store material, yet retains it anyways. On the other hand, continuous transfer is most often employed when material is repeatedly presented and gradually learned.
Once traces have been committed to LTS, they can be retrieved and brought forward to STS by either recognition or recall. The difference between these is best exemplified by the “tip of the tongue” phenomenon. Oftentimes, individuals find it difficult to recall a memory from LTS without further prompting. The recall of information is occasionally hindered by interferences from other stimuli, which can occur during coding or retrieval. When given a cue, relevant information becomes available through the process of recognition. The recognition of one trace brings forward others through associative processes. The explanation for this phenomenon is rooted in the belief that many partial traces are coded in LTS through their association with existing complete traces. The idea that traces do not have to be stored “all or none” fashion is supported by the observation that a second guess is often correct and not based completely on chance when attempting to recall specific fragments of information (Binford & Gettys, 1965).

The control processes utilized when coding, as previously mentioned, are transient events managed by the subject and influenced by either the subject’s personal history or the nature of the task at hand. These processes consist of schemes, coding techniques, and mnemonics that increase the efficacy of encoding and retrieving memories. At the level of the sensory register, individuals typically employ a scanning process to determine which senses they will devote attention to. The rehearsal of information regenerates STS traces and allows time for coding processes that assist in the transfer to LTS to operate. However, there is a trade off between the buffer size of STS and the ability to encode this information for LTS. While a large buffer size enables the individual to retain more information in STS, it hinders the ability to accurately transfer
this information to LTS. Put simply, the mind is so focused on maintaining a large quantity of information that there is a reduction in the quality of encoded information. Conversely, a small buffer size limits the amount of information in STS but allows for a more accurate encoding process.

When retrieving information from STS, it is more efficient for individuals to employ a quick search along ordered dimensions, or to list facts in an organized manner rather than at random. If partial decay has already occurred, it is often necessary to retrieve associated traces from LTS to generate a complete idea. Information from the sensory register can only enter STS indirectly, a process that is most effective if traces have been accurately encoded in LTS. When a stimulus is presented, the brain must perform a LTS search for previously encoded associations to this stimulus. The need to create new associations can often be eliminated by relying on existing associations. Encoding information through existing associations decreases the area of memory that must be searched when attempting to retrieve information and protects against interference from succeeding sensory inputs. The length of the search and the control processes utilized when recalling information from LTS are indicative of the efficiency of that search. As with searches in STS, those in LTS must be performed along ordered dimensions and it is the nature of the task that typically determines the procedure that is utilized. Individuals must know what information to search for, where to search for it, and when to terminate unsuccessful searches.

*Working Memory Model*

Shortly after the proposal of the multi-store model of dichotomized memory, Baddeley and Hitch (1974) published the working memory model (Figure 3). In short,
working memory replaced simplistic STS by suggesting that there is an active maintenance of short-term information, which further organizes a trace according to the particular sense that it appeals to. The original model for working memory, which was proposed in 1974, consisted of three major components: a central executive, a phonological loop, and a visuo-spatial sketchpad. Baddeley and Hitch suggested that the phonological loop and visuo-spatial sketchpad passively hold traces of sensory information that can cycle back and forth to the central executive. Many years later, Baddeley revised the model to include an episodic buffer, which provided a link to long-term memory (Baddeley, 2000).

The phonological loop, which is controlled by the left hemisphere of the brain, maintains speech and acoustic information. When auditory stimuli are presented, memory traces can be held in the phonological store for up to two seconds. Individuals employ
articulatory rehearsal processes to recite and prevent the decay of this information. Covert verbalization, as opposed to speaking out loud, is typically used to carry out this process internally. Unlike the information stored in the phonological loop, the right hemisphere of the brain maintains the visual, spatial, and kinaesthetic information stored in the sketchpad. Because visual information is typically more difficult to remember than auditory information, it is often converted to speech using preexisting associations. For example, an individual that views a word on a page will typically recite this word to himself or herself in an attempt to memorize it, rather than simply relying on their memory of the image of the word.

Information from these subcomponents of the working memory model is actively directed to the central executive, which was initially proposed to support storage, provide an interface with long-term memory, and allocate attention towards different resources. Subsequently, Baddeley and Hitch adopted the model of a supervisory attention system (SAS), to explain how the central executive directs changes in behavior when adjusted planning is required. This revision to the working model removed storage from the central executive’s list of functions and designated the function of an interface with long-term memory to a component called the episodic buffer. Consequently, the central executive was left with the primary task of focusing and dividing attention towards executive processes. The episodic buffer acts as a multimodal temporary store that links traces from the phonological loop and visuo-spatial sketchpad to long-term memory in an effort to create meaningful ideas. The capacity of this buffer is limited to the amount of information that can be maintained simultaneously without decay. Through the flexible
integration of these traces, the episodic buffer is ultimately responsible for a state of conscious awareness.

**Memory During Development**

Long-term memory is subdivided into categories depending on if a memory is implicit or explicit in nature. Implicit memory is the unconscious retention of procedural information. Simply stated, these memories instruct us how to perform learned activities such as brushing our teeth, eating a meal, or driving a car. On the other hand, explicit memory is the intentional remembrance of declarative and factual information. Declarative memories are further divided into semantic memories and episodic memories. Semantic memories are made up of concept-based knowledge, ideas, and facts that are not drawn from personal experiences. For example, the knowledge that fish live in water or that the United States Capitol is located in Washington, D.C. is a semantic memory that can be explicitly recalled. Episodic memories are autobiographical events made up from one’s personal collection of experiences. Such memories could include the birth of a sibling or the first day of school. Together, these two subcategories make up long-term explicit memory.

Memory storage is a complex mechanism that is largely influenced by developmental maturation. Implicit memory, specifically priming, matures at a fairly young age and is often fully developed by the age of four (Russo, Nichelli, Gibertoni, & Corina, 1995). Priming, which is a unique and unconscious aspect of implicit memory, occurs when prior exposure to a stimulus influences later exposure to that stimulus. Children who have undergone some degree of priming typically perform better on picture fragmentation tasks, during which prior exposure to an object would help them to better
identify a partial picture of that object. Even so, the accuracy of implicit material recognition is limited in early years and increases with age (Parkin & Streete, 1988). Further, studies have shown that the processes utilized by children to encode and recall these memories differ from those employed by fully matured adults (Carroll, Byrne, & Kirsner, 1985).

Explicit memory develops significantly later than implicit memory. Despite this, the immature recollection of explicit memories often contributes to implicit memory performance (Cycowicz, Friedman, Snodgrass, & Rothstein, 2000). This is most commonly exhibited in priming through early autobiographical memories, which are established during childhood between the ages of three and eight (Nelson, 1989). For instance, a young child who possesses an autobiographical memory of their most recent birthday party could more accurately identify a fragmented picture of a birthday party. However, it is not until adolescence that the ability to accurately recollect personal experiences is fully functional. At this stage, individuals have cultivated personalized rehearsal strategies, possess a larger knowledge base, and have developed a self-awareness of their own capabilities and limitations with memory. These properties, amongst others, allow for the fine tuning of encoding and retrieval processes that become more efficient with age (Ceci & Howe, 1978).
PSYCHOLOGICAL IMPACT ON MEMORY

Neonatal seizures resulting from HIE often have long-term negative effects on cognitive development. In particular, patients commonly present with deficits in memory, verbal abilities, visual abilities, and executive functions. While animal models of these disorders thoroughly explain the physiological effects of seizures, they often fail to suggest exactly how these effects contribute to observable memory deficits later in life. To address this, the focus of this paper will now turn to our first set of hypotheses, in which we will address three main memory deficits and their relationship to existing psychological models for memory formation.

Hypothesis 1.1 – Breakdown of Executive Functions

Neonatal seizures frequently result in poor social conduct resulting from the breakdown of executive functions, a set of skills that regulates behavior. When executive functions are impaired, patients experience an inability to integrate past experiences with present actions. For example, a child who is scolded for inappropriate behavior lacks the ability to learn from his or her mistake. Because these integration deficits also correlate with the ability to self-monitor behavior, we can conclude that the shortcomings experienced in executive functions result from a failure within the central executive component of memory. As discussed, the central executive functions in the allocation of attention resources towards working memory. An impairment of the central executive’s ability to direct attention would presumably present as a lack of focus in the individual. In this case, the inability to retrieve, reflect upon, and manipulate information would most certainly result in the impairment of executive functions.
**Hypothesis 1.2 - Developmental Amnesia**

When patients present with later-life developmental amnesia, explicit and episodic memories of personal facts are affected. Despite this, semantic memories and working memory remain intact. Because these amnesic effects appear later on in life, we can conclude that this deficit does not result from difficulty encoding memories for storage, but perhaps from ineffective maintenance and retrieval. In this case, we could postulate that dysfunction occurs within the central executive, episodic buffer, or both. The central executive accesses the episodic buffer through the medium of conscious awareness. Thus, attention is managed. If attention is not efficiently regulated due to failure of the central executive, retrieval and reflection on information cannot be directed appropriately. Similarly, if developmental amnesia is due to a failure within the episodic buffer, episodic memories cannot be retrieved from long-term memory. Therefore, it is reasonable to construe that developmental amnesia resulting from HIE affects the maintenance and retrieval of memories through defects in the functions of both the central executive and the episodic buffer.

**Hypothesis 1.3 - Verbal and Visual Deficits**

Verbal and visual deficits are an additional concern for HIE-induced neonatal seizures. In these cases, it is semantic memory, not episodic memory, which is affected. As in the case of developmental amnesia, individuals experience no challenge in learning new material but struggle to successfully carry out the transfer phase. When familiar information is presented with new features or in novel combinations, patients fail to associate these modified tasks to the previous ones. The deficit in recall stems from the inability to utilize information residing in the phonological loop and visuospatial
sketchpad when conducting LTS searches for previously encoded associations. Impaired control processes prevent patients from performing efficient searches and relating new information to existing memories. In short, these individuals must create entirely new memories without utilizing valuable associations with previously encoded memories.
BIOLOGICAL EFFECTS OF NEONATAL SEIZURES

With any abstract psychological phenomena, there are underlying neural substrates that provide explanation for clinical observations. To fully understand the origin of the cognitive deficits that result from neonatal seizures, we must explore how seizure activity affects brain function at a molecular level. We will now present a second set of theories that explain how synaptic plasticity at the neuronal level influences the behavioral plasticity that is necessary for memory formation. However, before we can delve into the neural substrates of memory we must first review the physiological effects of seizures.

*Altered Electrical Activity*

During seizures, neurons abandon normal function and begin to fire in sporadic bursts of activity, inhibiting normal brain function. Depending on the area of the brain involved, patients may exhibit varied states of consciousness (Cavanna & Monaco, 2009). If only an isolated portion of the brain is affected, then some degree of consciousness may be preserved, indicating a more positive long-term outcome. In the case of HIE-induced seizures, a chronic period of ischemia and consequent hypoxia continually deprives neurons of the substrates needed for cellular metabolism. When this occurs during the neonatal stage, the immature brain responds by inducing a complete and rapid necrosis of the affected tissue (Shin, Hong, Taem, & Kim, 2002). If these effects are progressive over time, cerebral blood flow in the affected region of the brain may be significantly altered, including changes in venous pressure, arterial pressure, etc (Shin et al., 2002).
Calcification from Atrophy

After recurrent exposure to hypoxic conditions, the affected region of the brain may begin to atrophy, resulting in an overall reduction of tissue volume (Jensen, 2009). Atrophy from neonatal seizures is characterized by a decrease in neuronal size as well as a loss of synaptic connections between neurons, contributing to a decrease in functional capabilities. Additionally, atrophy from HIE often results in the calcification of ischemic lesions. As detailed in a review by Ansar, Chincanchan, and Armstrong (1990), HIE causes a rapid decay of the extracellular Ca\(^{2+}\) gradient, which plays a significant role in the propagation of normal action potentials. Hypoxic conditions cause large quantities of extracellular Ca\(^{2+}\) to rapidly flow into the cell, where it is taken up by mitochondria. This drastic increase in mitochondrial Ca\(^{2+}\) inhibits normal function, ultimately resulting in necrosis and irreversible cell death.

Decreased Synaptic Plasticity

Overall the increased propensity to seizures during the neonatal period results from heightened neuroexcitability and augmented potential for synaptic plasticity. When hypoxic conditions contribute to a general reduction in both the size and function of affected regions, the developing brain exhibits a decreased potential for synaptic plasticity. Long term potentiation (LTP), a process that is widely accepted to play a role in learning and memory, is associated with a change in synaptic strength in response to varied levels of transmission. Seizure-induced alterations in LTP during critical developmental stages commonly result in the aforementioned cognitive, behavioral, and motor deficits that plague patients far beyond childhood.
NEURAL SUBSTRATES OF MEMORY

The potential for plasticity, both at a synaptic and behavioral level, is highest during early developmental periods, particularly the perinatal period that lasts from the 22nd week of gestation until seven weeks after birth (Nagy, 2011). Synaptogenesis begins during the sixth gestational week and undergoes a prominent increase during the two months before and after birth (Silverstein & Jensen, 2007). Initial encounters with sensory stimuli induce fine-tuning of the neural circuit, and these connections are strengthened by subsequent encounters (Hebb, 1949). The variation of responses to both novel and previously encountered stimuli are influenced by trace memories from prior experiences. These associations between stimuli are built into memory and are the basis for the capacity to learn. The following sections will examine the various structures associated with memory formation, as well as the molecular processes that occur within these structures.

Anatomical Structures

The process of encoding information as a memory is complex and involves a large number of anatomical structures. Because the first step in memory storage, regardless of the model employed, involves the registration of sensory input, virtually every lobe of the cortex is involved. The parietal lobe assists in the internal mediation of attention when filtering input (Berryhill, Chein, & Olson, 2011). Further, it can facilitate recall but cannot incorporate external cues into recognition (Dobbins, Jaeger, Studer, & Simons, 2012). The frontal lobe functions in coordination of behaviors, working memory, and non-task based long-term memories. Studies have found that epileptics with frontal
lobe damage must recruit wider areas of the brain when encoding memories for storage (Centeno et al., 2012). In the temporal lobe, domain specificity, which suggests there are specialized learning devices for different aspects of cognition, plays a significant role in the recognition of information from cues. This function is critically important to the ability to draw on associations between memories (Staresina, Cooper, & Henson, 2013). While the perirhinal cortex is devoted specifically to object-processing, the parahippocampal cortices are specific to scene-processing. One of the most striking associations between an anatomical structure and memory formation occurs within the cerebellum, which functions in the acquisition and storage of procedural memory. When cerebellar degeneration occurs, the degree of cellular atrophy directly correlates with the reduced capacity for motor learning (Thieme et al., 2013).

The limbic system is perhaps the greatest contributor to both the formation of memories and the emotions associated with them (Prada-Alcala, Medina, Lopez, & Quirarte, 2012). It encompasses a collection of structures that lie beneath the cerebrum and on both sides of the thalamus. Two major components of the limbic system are the amygdala and the hippocampus. The amygdala contributes primarily to emotion and fear learning (Prada-Alcala et al., 2012; Ross & Slotnick, 2008). Conditioned fear learning leaves a trace in the basolateral amygdala. In storing these traces, individuals either associate the stimuli with fear or acclimatize themselves to suppress fear in future encounters. Interestingly, reactivation of this trace followed by suppressed fear can abolish this memory altogether, in essence, attenuating the connectivity of the fear circuit (Agren et al., 2012). Through the discovery of its participation in fear learning, the amygdala has been recognized as a structure essential for the aversion to emotionally
unpleasant experiences. The hippocampus, like the amygdala, is capable of associating an emotional response to a memory. A recent study by Bellace, Williams, Mohamed, and Faro (2013) found that the type of stimuli associated with emotional responses dictates the geographical location of where the memory is stored. While the right hippocampus generates emotional responses to visual stimuli, the left hippocampus constructs associations with auditory stimuli (Wimmer & Shohamy, 2012). In addition, the hippocampus functions in the consolidation of memories from STS to LTS, specifically those associated with spatial learning. When attempting to retrieve memories, fMRI studies have shown hippocampal activation is most significant during recall rather than during recognition (Rugg et al., 2012).

Despite the amygdala’s significant contribution to memory, the synaptic basis of memory provided in this paper will focus specifically on studies performed in the hippocampus. The hippocampus is unique in that it has the capacity to store large quantities of unrelated information as well as self-generate temporally evolving memories, those that continue to be modified over time (Buzsáki & Moser, 2013). Early hippocampal activation indicates that there is a rapid recruitment of memory processes within this structure that enables memory retrieval (Horner et al., 2012). During hippocampal activity, theta waves and slow oscillations drive the preferential firing of hippocampal cell assemblies (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011). Through the propagation of these waves to other structures, the hippocampus regulates the exchange of information with nearby structures.

Memory consolidation, the process of preparing traces for LTS, has been most extensively studied in the CA1 region of the hippocampus, one of four subdivisions in the
cornu ammonis. The hippocampus receives the majority of its input from the entorhinal cortex and is believed to be largely responsible for memory formation and consolidation, processes that are frequently studied by examining spatial memory in rats. Information from the entorhinal cortex travels via the perforant pathway to the dentate gyrus, CA3, CA1, or the subiculum. Hippocampal studies often focus most closely on a pathway known as the trisynaptic circuit (Figure 3). In this circuit, information passes from granule cells of the dentate gyrus to CA3 pyramidal neurons via mossy fibers. Neural transmission runs through CA3 axons to CA1 pyramidal neurons via Schaffer collaterals. Axons from CA1 synapse in the deep layers of the subiculum, where information can loop back around to the entorhinal cortex or pass to the fornix. Because the trisynaptic circuit has been widely recognized for its role in memory formation, it is important to understand the physiologic changes that take place in these neurons.

Figure 3. Schematic of the neural circuitry within the trisynaptic circuit of the hippocampus
**LTP and AMPA Receptor Cycling**

As mentioned, LTP is an imperative process in the maintenance of synaptic plasticity, during which synapses undergo a change in strength in response to varied levels of transmission. These changes often directly correlate with the size of the postsynaptic density (PSD), number of receptors, and amount of neurotransmitter released. Since both learning and memory formation are believed to result from synaptic plasticity, it is widely accepted that LTP plays a major role in these processes.

Neurotransmission begins when a depolarizing action potential propagates to the terminal of a presynaptic axon. As depicted in Figure 4, presynaptic vesicles are exocytosed from the axon terminal and their contents diffuse across the synaptic cleft. The concentration of neurotransmitter in the synaptic cleft remains high for only a short time, resulting in brief synaptic currents (Luscher & Malenka, 2012). Whereas receptors on the presynaptic side participate in a feedback mechanism that modulates neurotransmitter release, those on the postsynaptic dendrites bind neurotransmitters to elicit a variety of cellular responses.

![Figure 4. Depiction of synaptic neurotransmission that occurs during LTP (Sadava, 2008)](image)
During LTP, glutamate, an important neurotransmitter, is released from the presynaptic axon and binds to two types of ionotropic receptors: N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. These receptors directly form ion channel pores, unlike metabotropic receptors that indirectly link with ion channels on the plasma membrane through signal transduction mechanisms. Both NMDARs and AMPARs are permeable to a strong inward current of \( \text{Na}^+ \) and a weak outward current of \( \text{K}^+ \), in addition to a \( \text{Ca}^{2+} \) current. AMPARs carry a net inward current at negative potentials and a net outward current at positive potentials.

AMPARs are either a homomeric or heteromeric mixture of four possible subunits: GluA1, GluA2, GluA3, and GluA4. While homomeric AMPARs contain only one type of subunit, heteromeric AMPARs consist of two sets of symmetric subunits. The hippocampus, which is the primary site of LTP, is characterized by heteromeric AMPARs containing GluA2, along with either GluA1, GluA3, or GluA4 (Kauer & Malenka, 2006). The GluA2 subunit is unique in that it undergoes RNA editing after transcription, during which the codon for a glutamine residue in the ion channel pore is replaced by a codon for arginine (Luscher & Malenka, 2012). This exchange of codons enables the subunit to move out of the endoplasmic reticulum where it can be incorporated into the AMPAR. The size of the arginine residue in modified GluA2 subunits prevents the passage of divalent ions such as \( \text{Ca}^{2+} \). As a result, AMPARs lacking GluA2 are permeable to \( \text{Ca}^{2+} \) and have an inward-rectifying current.

Synapses that contain NMDARs with few to no AMPARs are considered “silent,” as their ability to transmit depolarizing action potentials is significantly impaired. The
silent synapse hypothesis, which states that AMPARs are recruited to inactive synapses by the induction of LTP, is based on the belief that NMDARs are capable of detecting twice the quanta of glutamate that can be detected by AMPARs (Kullmann, Asztely, & Walker, 2000). In theory, LTP can be modulated by NMDARs alone if the amount of glutamate released from the presynaptic axon terminal is insufficient to open the AMPARs located on the membrane. However, NMDARs are occluded by an Mg$^{2+}$ block that requires depolarization to be expelled. As a result, the flow of Na$^+$, K$^+$, and Ca$^{2+}$ through the cell is a voltage-dependent process. Thus, accentuating the need for AMPARs, which drive synaptic signaling.

It has been mentioned that the absence of AMPARs renders the synapse silent. Therefore, it is reasonable to conclude that AMPARs are recruited to the membrane during LTP. During cycling, AMPARs come from a reserve pool of receptors that are stored within early endosomes (Park, Penick, Edwards, Kauer, & Ehlers, 2004). AMPAR degradation within neurons is regulated in an activity-dependent manner that is specific to both the type of subunit receptor and the nature of its internalization, the process of endocytosing AMPARs from the synaptic membrane. AMPA-induced internalization causes GluA2 subunits to enter the recycling pathway. However, NMDA-induced internalization causes GluA2 subunits to be sent to late endosomes and lysosomes for degradation. On the other hand, this same type of internalization causes GluA1 to remain active in the recycling pathway (Lee, Simonetta, & Sheng, 2004). Further, the source of AMPARs during cycling induced by LTP has been confirmed by studies using mutants that prevent endocytotic translocation to the plasma membrane. In these cases, the overall expression of AMPARs was significantly decreased (Park et al., 2004). AMPAR cycling
is regulated by the Ca\(^{2+}\)-induced activation of Ca\(^{2+}\)/calmodulin-dependent protein kinase II (CaMKII) and protein kinase A (PKA), which phosphorylate serine residues on the AMPAR subunits. The phosphorylation of serine 831 (S831) and serine 845 (S845) sites on the GluA1 subunit during the induction of LTP causes these subunits to be inserted to the plasma membrane (Santos, Carvalho, Caldeira, & Duarte, 2009). Interestingly, this process depends largely on the history of the synapse itself. Immature or previously depressed synapses can experience an intense upregulation of serine residue phosphorylation upon the administration of high frequency stimulation (Lee et al., 2004). However, these subunits are not delivered directly to the PSD and require NMDA activation for their localization (Santos et al., 2009). Lipid membrane and proteins accompany the delivery of GluA1 subunits, which explains why AMPAR cycling plays a vital role in the increase of both synaptic strength and size.
PHYSIOLOGICAL IMPACT ON MEMORY

Because LTP is viewed as a long-lasting enhancement of synaptic transmission, it is no surprise that seizure activity, which is characterized by sporadic and uncoordinated synaptic excitation, has an effect on this process. The risk for seizures is highest during the neonatal period, a critical time for synaptic development, during which dendritic processes are constantly expanding and retracting, sampling their environment for potential synaptic partners (Cline & Haas, 2008). During this time, the expression of ionotropic glutamate receptors is at its peak and contributes to the neonate’s increased susceptibility to seizures. In the hippocampus beginning in the first postnatal week, the synapses gradually become functional as purely NMDAR-based synapses, silent synapses, are converted to functional AMPAR/NMDAR synapses. This transformation is input specific and dependent upon the occurrence of LTP (Durand, Kovalchuk, & Konnerth, 1996). The increase in the number of activated receptors modulates the increase in amplitude of excitatory post-synaptic currents (EPSCs) (Stubblefield & Benke, 2010).

Hypothesis 2.1 - Induction and Saturation of LTP

The excitability observed during seizure activity induces LTP by stimulating AMPAR cycling. Phosphorylation of the GluA1 and GluA2 subunits is evident shortly after seizures, resulting in hyperexcitability that increases sensitivity to future seizures. This excitability may reduce the number of silent synapses present in the neonatal brain by recruiting AMPARs to the plasma membrane.
Early studies investigating the connection between seizures and synaptic plasticity examined the effects of electroconvulsive therapy (ECT) on cognitive function. ECT, an early form of treatment for severe affective disorder, was administered via electrical seizure induction. Patients undergoing ECT reported difficulty in learning new material for up to six months after treatment, especially when multiple seizures were induced (Reid et al., 1997). Additional studies performed using adult male hooded Lister rats aimed to emulate these effects through the induction of electroconvulsive seizures (ECS) (Reid et al.). The study showed that the amplitude and frequency of excitatory postsynaptic potentials (EPSPs) associated with LTP increased with each application of ECS, stabilizing around 4-5 seizures. However, when the researchers attempted to induce LTP following the seizures, the rats showed impaired performance in their ability to form memories regarding spatial bias in a water maze. Overall, the over expression of EPSPs resulted in decreased LTP. From this, it can be concluded that ECS itself induces LTP and saturates its mechanism of action in a widespread and indiscriminate manner, reducing overall synaptic potential.

**Hypothesis 2.2 - Increased Phosphorylation of AMPA Receptors**

More recent studies have focused on the effects of seizures on synaptic plasticity in neonates, who are undergoing a period of critical synaptic development and have the potential to experience long-term effects. In subjecting postnatal day 10 (P10) rat pups to hypoxia-induced seizures (HS), Rakhade et al. (2008) demonstrated an increase in the amplitude of AMPAR-mediated excitatory postsynaptic currents (EPSCs) from CA1 pyramidal neurons. The observed changes in EPSCs correlated with increased phosphorylation of the S831 and S845 sites on GluA1. Therefore, it is reasonable to
conclude that increased AMPAR-mediated currents were a result of increased GluA1 phosphorylation.

In addition to the alterations experienced by GluA1, HS appeared to cause a significant increase in the phosphorylation of GluA2. P10 rat pups naturally have Ca\(^{2+}\) permeable AMPARs due to decreased GluA2 expression. HS further decreased the expression of GluA2 on the synaptic membrane 48 hours after stimulation via phosphorylation of the serine 880 (S880) site, resulting in GluA2-lacking AMPARs that produced an inward rectifying current. PKA and CaMKII are responsible for the phosphorylation of S845, while protein kinase C (PKC) phosphorylates both S831 and S880 (Santos et al., 2009). Since increased stimulation of LTP correlates with an increase in the phosphorylation of S831, S845, and S880, it is reasonable to suspect that increased activity of PKA, CaMKII, and PKC is also observed. Further, it was found that the GluA2-lacking AMPAR antagonist philanthotoxin was capable of blocking LTP if applied before and during stimulation (Plant et al., 2006). Combined, these results provide further evidence that the Ca\(^{2+}\) flow permitted by GluA2-lacking AMPARs is necessary for the induction of LTP during development.

Hypothesis 2.3 - Reduction of Silent Synapses

Because studies have established that the HS-stimulated increase in phosphorylation of AMPAR subunits caused a profound effect on LTP, it can be hypothesized that the phosphorylation induced by HS may alter the fraction of silent synapses present on the postsynaptic membrane. Silent synapses, which lack AMPARs altogether, are characterized by a large failure rate when attempting to evoke EPSCs at negative membrane potentials of -55mV to -65mV (Rakhade et al., 2008). A study by
Zhou, Lippman, Sun, and Jensen (2011) noted that as predicted, the ratio of silent to functional synapses in P10 rat pups was reduced during HS. The possibility of Mg\(^{2+}\) insensitivity was ruled out as a factor, indicating that NMDARs did not contribute to the failure rate of EPSCs used to calculate these ratios (Zhou et al., 2011). Additionally, the effects of hypoxia alone were found to be negligible due to the lack of difference between hypoxic pups that did not experience seizures and the control group. Together, these results suggest that HS diminished silent synapses by simply introducing AMPARs to the membrane.

Further, HS appeared to increase the colocalization of AMPARs and NMDARs across the membrane. Synaptophysin, GLUR1, and NR1, functional subunits from each receptor, were triple immunolabeled to detect the presence of NR1 puncta that were in contact with both synaptophysin puncta and GLUR1 puncta (Zhou et al., 2011). HS decreased the percentage of synapses containing only contacts between NR1 puncta and synaptophysin puncta, indicating that HS decreased the number of silent synapses (Zhou et al., 2011). The reduction in silent synapses by increased colocalization can be inferred to be a result of AMPAR subunit phosphorylation, which ultimately moves AMPARs to the membrane. It is important to note that these processes occur during normal stimulation of LTP. However, the occurrence of a seizure magnifies these effects and unnecessarily induces LTP in an unregulated manner. In effect, seizures saturate the mechanism and inhibit the ability to induce LTP during actual learning and memory formation.
CONCLUSION

Neonatal seizures, particularly those due to HIE, are a significant problem in both term and pre-term infants and are influenced by a variety of inherent risk factors. Neonates exhibit the highest proclivity to seizure activity due to their heightened potential for neuroexcitation, a property that has a profound impact on the potential for synaptic plasticity. Early life neonatal seizures are commonly associated with long-term cognitive impairments, such as those seen in learning and memory. While not classified as an epileptic disorder, the occurrence of seizures during the neonatal period increases susceptibility to epilepsy far into adulthood.

Through a comprehensive understanding of existing memory paradigms, such as Atkinson and Schiffrin’s multi-store model and Baddeley and Hitch’s working memory model, we can begin to explain how neonatal seizures result in impaired executive function, verbal and visual function, and memory storage processes. During this critical time for development, seizure activity alters the function of memory components that are critical to both STS and LTS. Additionally, seizures disrupt the control processes used when attempting to process sensory stimuli, to prevent the decay of traces from STS, and to retrieve memories from LTS. From this, we can deduce that the apparent memory damage resulting from neonatal seizures is attributed to the third model proposed by Martinos et al. (2012) in an effort to explain the source of cognitive dysfunction. In this model, it is suggested that both an inherent predisposition to neonatal seizures, as well as the seizure itself, contribute to the cognitive deficits seen in these individuals.

On a physiologic level, the impairments seen in these individuals can be explained through the relationship between memory formation and LTP. LTP, a process
that is widely accepted to play a role in learning and memory, is associated with a change in synaptic strength in response to varied levels of transmission. Alterations in LTP during critical developmental stages commonly result in cognitive, behavioral, and motor deficits that plague patients far beyond childhood. Rat studies have found that HIE-induced seizures induce the activation of various kinases that phosphorylate serine residues on AMPAR subunits. This process triggers the mobilization of AMPARs to the synaptic membrane, thus decreasing the ratio of silent to active synapses and allowing for heightened synaptic potential. Overall, these studies have found that seizure activity overstimulates LTP, thus saturating its mechanism and reducing the potential for effective memory storage. Thus, resulting in many forms of memory impairment and cognitive setbacks.

In this paper, we have presented two related, yet distinctly separate sets of hypotheses that explain the cognitive deficits from seizures by means of both psychological and physiological perspectives. Using the various STS and LTS components from existing memory models, we have explained the theoretical basis of seizure-induced cognitive deficits. Additionally, we have used findings from studies at a synaptic level to propose an association between the neural substrates of memory and the neural substrates of seizures. However, the direct relationship between these neural substrates and the memory components that they ultimately affect is beyond the scope of this paper and future studies are needed to more clearly elucidate this relationship.
BIBLIOGRAPHY


