Anatomical, Physiological, and Pharmacological Properties Underlying Hippocampal Sensorimotor Integration.

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The sensorimotor model of hippocampal formation was last updated in a review by Bland and Oddie (2001). The model asserts that components of the neural circuitry in hippocampus and associated structures function in the capacity of providing voluntary motor systems with continually updated feedback on their performance relative to changing environmental (sensory) conditions. A crucial aspect of this performance is the intensity with which the motor programs are initiated and maintained. The components of the neural circuitry involved in sensorimotor integration are those underlying the production of oscillation and synchrony (theta) in the hippocampus and associated structures. Significant additions to the updated review included the description of the ascending brainstem hippocampal synchronizing pathways as the anatomical basis of the model, with the posterior hypothalamic region assigned the role of providing motor feedback to the hippocampal formation. A significant proportion of the nuclei contributing to the ascending brainstem hippocampal formation synchronizing pathways, up to and including the hippocampus, are cholinergic, cholineptive, or both. The objective of the present chapter is to update the sensorimotor integration model, with particular emphasis on the incorporation of two areas of research that have shown rapid development in the last few years: (1) the demonstration of a glutamate pathway as the third major septohippocampal projection, along with cholinergic and GABAergic
projections; (2) the detailed description of the median raphe nucleus as the main origin of the ascending brainstem hippocampal desynchronizing pathways, and its functional implications.

**The cellular basis of theta band oscillation and synchrony**

The limbic cortex represents multiple synchronizing systems (Bland & Colom, 1993). Populations of cells in these structures display membrane potential oscillations (MPOs) as a result of intrinsic properties of membrane currents. These cells also receive inputs from other cells in the same structure and inputs from cells extrinsic to the structure, many of the latter from nuclei contributing to the ascending brainstem hippocampal synchronizing pathways. Theta-band oscillation and synchrony in the hippocampal formation (HPC) and related limbic structures is recorded as an extracellular field potential consisting of a sinusoidal-like waveform with an amplitude up to 2 mV and a narrow band frequency range of 3 – 12 Hz in mammals. The asynchronous activity termed large amplitude irregular activity (LIA) is an irregular waveform with a broadband frequency range of 0.5 – 25 Hz (Leung et al. 1982). Kramis et al. (1975) were the first to formally propose the existence of two types of hippocampal theta activity, in both the rabbit and the rat (see review by Bland, 1986). One type was termed atropine-sensitive theta, since it was abolished by the administration of atropine sulfate. Atropine-sensitive theta occurred during immobility in rabbits in the normal state and occurred in both rabbits and rats during immobility produced by ethyl ether or urethane treatment. The other type of theta was termed atropine-resistant, since it was not sensitive to treatment with atropine sulfate but was abolished by anesthetics. Atropine-resistant theta was the movement related theta originally described by Vanderwolf (1969) and is thought
to be sensitive to serotonin antagonists (Vanderwolf and Baker, 1986). Since atropine-sensitive theta became operationally defined as theta occurring during one example of a Type 2 behavior, i.e. immobility, it became known as Type 2 (immobility-related) theta. Atropine-resistant theta became known as Type 1 theta, since it occurred during Type 1 (voluntary) motor behaviors, such as walking, rearing, and postural adjustments (Vanderwolf, 1975). Type 2 theta thus originally became operationally defined as theta that occurred in the complete absence of movement. The sensorimotor integration model assumes that Type 2 theta in the HPC is the electrical sign of processing sensory stimuli that are relevant to the initiation and maintenance of voluntary motor behaviors and that it is always coincidently active whenever the Type 1 theta subsystem is active. Thus, an animal may be immobile and generate Type 2 theta in isolation, but whenever Type 1 movements occur, Type 2 theta is always occurring coincidently. As discussed below, there is evidence for a septohippocampal glutamatergic system being involved in theta generation and behavior.

Many populations of cells in the HPC and related structures exhibit discharge properties that are precisely related to hippocampal theta field activity. Such theta-related cells comprise two distinct populations termed theta-ON and theta-OFF, first described in acute preparations by Colom et al. (1987), followed by a detailed cell classification paper by Colom and Bland (1987) and subsequently used to classify theta-related cells in the HPC in a number of studies (Bland and Colom 1988, 1989; Colom et al. 1991; Smythe et al. 1991; Konopacki et al. 1992, 2006; Bland et al. 1996; McNaughton, et al 1983; Mizimori, et al (1990). Theta-ON and theta-OFF cells have also been recorded in the medial septal nucleus and nucleus of the diagonal band of Broca (MS/vDBB) (Ford et al.
1989; Bland et al. 1990; Colom and Bland 1991; Bland et al. 1994), the entorhinal cortex (Dickson et al. 1994, 1995), cingulate cortex (Colom et al. 1988), caudal diencephalon (Bland et al. 1995; Kirk et al. 1996), median raphe nucleus (Viana Di Prisco, et al., 2002), rostral pontine region (Hanada et al. 1999), the superior colliculus (Natsume et al. 1999), the basal ganglia (Hallworth and Bland, 1999), the red nucleus (Dypvik and Bland, 2004) and the neocortex (Lukatch and MacIver 1997). Theta-ON cells increase their activity during theta field activity as reflected by an overall mean increase in discharge rate or as a linear positive increase in discharge rate in relation to increasing frequencies of simultaneously recorded theta field activity. Theta-OFF cells decrease their activity during theta field activity as reflected by an overall mean decrease in discharge rate (to zero in many cases) or by a linear negative increase in discharge rate as theta field frequency declines. A further criterion relates to the pattern of cell discharges. A given theta-related cell discharges in one of two characteristic patterns during theta field activity. The first is a rhythmic bursting pattern we have termed phasic, since each cell burst occurs with a consistent phase relation to each cycle of theta field activity. The second pattern is either regular or irregular discharges we have termed tonic, since they consist of a non-bursting discharge pattern with no consistent phase relation to theta field activity. Both theta-ON and theta-OFF cells have phasic and tonic subtypes. The rhythmic discharges of all phasic theta-ON cells during Type 2 theta was abolished by the administration of atropine sulfate, and are therefore mediated by ACh. The inhibition of all phasic theta-OFF cells during Type 2 theta was resistant to the administration of atropine sulfate. Theta-ON and theta-OFF cells represent a general organization of the
cellular mechanisms underlying “theta band” oscillation and synchrony in the HPC and related structures.

Theta-band oscillations may also be recorded intracellularly in some populations of cells in the HPC, during the simultaneous occurrence of the extracellular theta field oscillations. In agreement with previous work (Leung and Yim 1991) we adopted the term membrane potential oscillations (MPOs) to designate the slow intracellular oscillations that occur at theta frequencies in subsets of hippocampal cells. The occurrence of MPOs in HPC pyramidal cells, dentate granule cells and interneurons has been well documented (Bland et al. 1988; Bland, et al., 2002; Bland, et al., 2005; Chapman and Lacaille 1999; Fox et al. 1983; Fox 1989; Fujita and Sato 1964; Konopacki et al. 1992 Leung and Yim 1986, 1988, 1991; Leung and Yu 1998; Nunez et al. 1987; Nunez et al. 1990a,b, c; MacVicar and Tse 1989; Munoz et al. 1990; Ylinen et al. 1995). The morphological identity of theta-ON and theta-OFF cells is crucial to the understanding of the cellular interactions involved in the generation of theta field activity. Earlier studies by Fox and Ranck (1975, 1981) provided indirect evidence that theta cells (theta-ON cells in our scheme) in the HPC were interneurons, a view supported by some recent work on identified cells (see review by Buzsaki 2002). On the other hand, Bland and Colom (reviewed in Bland and Colom 1993) proposed, also based on indirect evidence, that a sub-population of HPC projection cells (pyramidal and granule cells) were theta-ON cells and a sub-population of HPC interneurons were theta-OFF cells. More recent work by Bland, et al. (2002) provided evidence supporting the following conclusions concerning cells classified as phasic theta-ON cells: (1) morphologically identified hippocampal CA1 (see Figure 1) and CA3 pyramidal cells represent
CA1 PYRAMIDAL PHASIC THETA-ON CELL

A.

B.

C.

a subset of cells meeting the criteria for classification as phasic theta-ON cells,
supporting the findings of a number of previous studies (Fujita and Sato 1964; Nunez et
al. 1987, 1990a; Leung and Yim 1988, 1991); (2) MPOs occurred only during theta field activity, their onset signaled by a 5 – 10 mV depolarizing shift in membrane potential; (3) the amplitude of membrane potential oscillations in CA1 pyramidal phasic theta-ON cells was voltage-dependent and frequency was voltage independent; (4) There were no phase changes observed during current injections, however amplitude analysis of MPOs revealed an inverted U-shaped curve asymmetrically distributed around the average value of the membrane potential occurring during the spontaneous theta (no current) control condition; (5) The rate of rhythmic spike discharges in the CA1 pyramidal phasic theta-ON cells during the theta condition was precisely controlled within a critical range of membrane potential values from approximately –57 to –68 mV, corresponding to a range of MPO amplitudes of approximately 4 to 7 mV. Outside the critical range, rhythmical discharges were abolished. Also in that study, 22 cells met the criteria for classification as phasic theta-OFF cells and provided evidence to support the following conclusions: (1) morphologically identified CA1 pyramidal layer basket cells (see Figure 2), mossy hilar cells, and granule cells formed a subset of cells meeting the criteria for classification as phasic theta-OFF cells;
(2) MPOs occurred only during theta field activity, their onset signaled by a hyperpolarizing shift of 5 – 10 mV in membrane potential; (3) the amplitude of membrane potential oscillations in CA1 pyramidal layer basket cells was voltage
dependent and frequency was voltage independent; (4) the phase of membrane potential oscillations in CA1 pyramidal layer basket cells underwent an approximately 180° phase reversal when the membrane potential was depolarized to around –65 mV; (5) the occurrence and rate of rhythmic spike discharges in the CA1 pyramidal layer basket cell phasic theta-OFF cells during the theta condition was precisely controlled within a critical range of membrane potential values from approximately –62 to –60 mV, corresponding to a range of MPO amplitudes of approximately 7 to 7.5 mV. Outside the critical range, spikes were absent or occurred singly. In a subsequent intracellular recording and labeling study, Bland, et al. (2005) demonstrated that hippocampal pyramidal cells were functionally heterogeneous in relation to the generation of theta-band oscillation and synchrony. In field CA1 pyramidal cells formed theta-related subsets of phasic theta-ON cells and tonic theta-ON cells and non theta-related subsets of simple spike discharging cells, complex spike discharging cells and “silent” cells. Similar findings were evident for CA3 pyramidal cells. Recently, in an amazing technical breakthrough, Lee, et al. (2006) were able to carry out whole-cell recording of a CA1 pyramidal cell in a freely moving rat. During a head movement the membrane potential displayed oscillatory (MPOs) activity in the theta frequency range, thus verifying our results in hippocampal slices and acute anesthetized preparations.

The ascending brainstem hippocampal synchronizing pathways.

The rostral pontine region

Experiments utilizing electrical stimulation techniques revealed that the origins of the ascending brainstem hippocampal synchronizing pathways were the nucleus reticularis pontis oralis (RPO) and the pedunculopontine tegmental nucleus (PPT) (Macadar,
Chalupa, and Lindsley, 1974; Vertes, 1981; Oddie, Bland, Colom, and Vertes 1994; Vertes, Colom, Fortin, and Bland, 1993; Vertes and Kocsis, 1997; Bland and Oddie, 1998). Vertes, Colom, Fortin, and Bland (1993) also demonstrated that microinjections of the cholinergic agonist carbachol into the RPO and PPT were very effective in eliciting theta field activity in the HPC. Subsequently, Bland, Oddie, Colom, and Vertes (1994) showed that either electrical stimulation or the microinfusion of carbachol administered to the RPO resulted in the intense activation of phasic and tonic theta-ON cells in the medial septal nuclei and the nucleus of the vertical limb of the diagonal band of Broca (MS/vDDB). Kirk, Oddie, Konopacki, and Bland (1996) investigated the effects of electrical stimulation of the RPO on hippocampal field activity and the activity of cells in the posterior diencephalic region. They showed that electrical stimulation of the RPO produced theta field activity in the hippocampus and a regular non-bursting (tonic) increase in the discharge rate of the posterior hypothalamic (PH) cells, as well as a rhythmic bursting pattern of cells in the supramammillary (SUM) and medial mammillary (MM) nucleus. All studies to date investigating cellular activity in the nuclei of the RPO and PPT in relation to hippocampal theta generation have revealed only irregular (tonic) discharge patterns (Vertes, 1977, 1979; Siegal, McGinty, and Breedlove 1977; Nunez, de Andres, and Garcia-Austt 1991; Hanada, Hallworth, Szigatti, and Bland, 1999). Nunez, de Andres, and Garcia-Austt (1991) also reported similar discharge patterns in 18 RPO cells recorded during hippocampal field activity evoked both by sensory stimulation and by microinjections of carbachol into the pontine region. Subsequent injection of atropine abolished the carbachol effects.
The caudal diencephalic region

Fibers from the RPO and PPT ascend and synapse with caudal diencephalic nuclei, primarily the posterior hypothalamic (PH) nucleus and the supramammillary (SUM) nucleus (Vertes 1992; Vertes, Crane, Colom, and Bland 1995). Physiological and pharmacological studies support the view that the PH and SUM nuclei of the caudal diencephalon are a critical part of the ascending synchronizing pathways linking the rostral pontine region with the septohippocampal pathways. Kirk and McNaughton (1993) demonstrated that procaine infused into the SUM abolished HPC theta field activity produced by electrical stimulation of the reticular formation. Figure 3 from a study by Oddie, Bland, Colom, and Vertes (1994) illustrates that the microinfusion of procaine into the PH abolished the spontaneous occurrence of HPC theta field activity and the theta field activity produced in response to electrical stimulation of the RPO. The microinfusion of procaine into the PH also abolished the rhythmicity of all phasic theta-ON cells in the MS/vDBB that was previously induced by electrical stimulation of the RPO.
Oddie, et al. (1994) also showed that the microinfusion of carbachol into the PH and SUM region and resulted in the continuous generation of HPC theta field activity that
was higher in frequency than the mean frequency of spontaneously occurring theta and significantly larger in amplitude.

Electrical stimulation of the PH produces hippocampal theta activity, the frequency of which is linearly related to the intensity of hypothalamic stimulation (Bland and Vanderwolf, 1972a). Electrical stimulation of the PH also results in the intense activation of theta-ON cells in the MS/vDBB (Bland, Colom, and Ford, 1990; Bland, Oddie, Colom, and Vertes, 1994), the hippocampal formation (Colom, Ford, and Bland, 1987; Smythe, Christie, Colom, Lawson, and Bland, 1991), and the entorhinal cortex (Dickson, Kirk, Oddie, and Bland, 1995), as well as theta field activity in the entorhinal cortex (Dickson, Trepel, and Bland, 1994). In the Bland, Oddie, Colom, and Vertes (1994) study, five MS/vDBB phasic theta-ON cells were tested consecutively with electrical stimulation of the RPO and the PH and were shown to be activated in a similar manner in either condition. The intensity of activation of MS/vDBB cells by electrical stimulation of the RPO and PH was relayed on to theta-related cells in the HPC in a very precise manner. Colom, Ford, and Bland (1987) demonstrated by linear regression analysis that phasic theta-ON cells in the HPC translated the level of activation of the ascending synchronizing pathways through their discharge rates (shown in Figure 4). Figure 5 shows a phasic theta-OFF cell during the transition from higher frequency theta to lower frequency theta to LIA. Phasic theta-OFF cells were inhibited by PH stimulation and the inhibition was not abolished by the administration of atropine sulfate (shown in Figure 6).
CA1 LAYER PHASIC THETA-OFF CELL
(CELL 17-2)

HPC FIELD

THETA-OFF CELL

DECREASING THETA FREQUENCIES

L1A

1 sec

.5mV

.5mV
Studies investigating the discharge properties of theta-related cells in the caudal diencephalon have revealed both rhythmic and non-rhythmic patterns. Kirk and
McNaughton (1991) were the first to demonstrate, based on multiunit recordings, that cells in the SUM discharged in a rhythmically bursting pattern in phase with HPC theta field activity. Kocsis and Vertes (1994) verified this finding with single unit recordings in the SUM and, in addition, demonstrated that cells in the MM nuclei also discharged in a rhythmically bursting pattern in phase with HPC theta field activity. Bland, Konopacki, Kirk, Oddie, and Dickson (1995) characterized the discharge patterns of cells in specific nuclei of the caudal diencephalon in relation to simultaneously recorded field activity from the stratum moleculare of the dentate gyrus, according to the criteria of Colom and Bland (1987). Of 54 cells recorded in the posterior hypothalamic nucleus (PH) 43 (80%) were classified as tonic theta-ON and 11 (20%) as non-related. Tonic theta-ON cells in the PH discharged at significantly higher rates during theta, either occurring spontaneously or elicited with a tail pinch, than during LIA. Nine thalamic centromedial (CM) cells were recorded, seven of which were classified as tonic theta-ON cells and two of which were non-related (see Figure 7).
Twenty cells were recorded in the border region of the PH/SUM. Of these, 15 (75%) were classified as tonic theta-OFF cells discharging at significantly higher rates during LIA than during either spontaneously occurring theta or tail pinch-induced theta (see Figure 8). Five cells recorded in the PH/SUM border region were non-related.
All 16 cells (100%) recorded from the SUM were classified as phasic theta-ON cells. Unlike phasic theta-ON cells recorded in other brain regions, cells in the SUM did not significantly increase their discharge rate during the transition from LIA to theta field activity. Of the 23 cells recorded from the MM, 19 (83%) were also classified as phasic theta-ON cells and the remaining four cells were non-related (see Figure 9).
While theta related cells in the PH and SUM nuclei are activated by the ascending brainstem hippocampal synchronizing pathways, the production of rhythmic cell bursting in the MM appeared to be dependent on descending activation from the septohippocampal pathways (Kirk, Oddie, Konopacki, and Bland, 1996).

The medial septal region

The medial septal region (MS/vDBB) functions as the node of the ascending synchronizing pathways, distributing inputs to the posterior cingulate cortex, entorhinal cortex, and the hippocampal formation (Bland, 2000). The cholinergic septohippocampal
projection was the first pathway to be documented, using a variety of experimental
techniques, showing that HPC pyramidal and granule cells were the main recipients of
these cholinergic inputs (Frotscher and Leranth 1985). The activation of cholinergic
receptors on cells in the MS/vDBB through the microinfusion of carbachol resulted in the
production of theta field activity in the HPC in both acute (Oddie et al.1994) and freely
moving rats (Monmaur and Breton 1991; Lawson and Bland 1993). Smythe, Colom, and
Bland (1992) proposed that cholinergic and GABAergic projections originating in the
MS/vDBB act synergistically to modulate the synchronizing activity from the ascending
brainstem pathways. Cholinergic projections provide a steady tonic excitatory afferent
drive for HPC theta-ON cells, and GABAergic projections act to reduce the overall level
of inhibition by inhibiting HPC GABAergic interneurons (theta-OFF cells). Both
activities must be present for the generation of HPC theta field and cellular activities. The
balance between the cholinergic and GABAergic systems determines whether
hippocampal synchrony (theta) or asynchrony (LIA) occurs. Destruction of the medial
septal region completely abolished theta field activity in the HPC (Bland 1986). Bland
and Bland (1986) demonstrated that both Type 1 and Type 2 HPC theta field activity was
abolished in freely moving rabbits, along with theta-ON cell rhythmicity during both
these conditions.

Subsequent research led to the description of a GABAergic septohippocampal projection
(Misgeld and Frotscher 1986) and these projection form synaptic contacts on all
identified HPC interneurons and other "non pyramidal" neurons (Acsady, Halasy, and
Freund, 1993; Freund, 1989; Freund and Antal, 1988; Gulyas, et al., 1990; Meittinen and
Freund, 1992). Bland et al. (1996) microinfused the GABA-A agonist muscimol into the
MS/vDBB nuclei while recording hippocampal field and theta-ON cell activity occurring both spontaneously and in response to electrical stimulation of the PH, in urethane-anesthetized rats. The microinfusion of 5.0-12.5 nmol of muscimol resulted in the progressive reduction in the power (amplitude) and finally the total loss of hippocampal theta field activity. In contrast, the frequency of HPC theta remained unaffected during the entire postinfusion period that theta field activity was present. Overall, the effects of intraseptal micro infusions of muscimol on HPC theta field activity produced by electrical stimulation of the PH were the same as those reported for spontaneously occurring HPC theta field activity. In the time immediately following the first 1 min infusion of 5 nmol muscimol (before changes in theta amplitude occurred), a brief period of increased theta-ON cell excitability was observed, manifested as an increase in the number of discharges per burst. Associated with the progressive reduction of HPC theta amplitude, phasic theta-ON cell discharge rates progressively decreased. Just prior to the disappearance of theta, phasic theta-ON cells ceased discharging. During the period when HPC field activity was replaced with low amplitude asynchronous activity, however, phasic theta-ON cells discharged in bursts correlated with every occurrence of hippocampal sharp wave field activity. The loss of rhythmic bursting of hippocampal phasic theta-ON cells following the microinfusion of muscimol into the MS/vDBB paralleled the loss of theta amplitude. Bland et al. (1996) interpreted the results of the intraseptal infusion of muscimol on HPC theta field and cellular activity in the following manner: The brief excitatory effect on hippocampal theta-ON cell discharges may be correlated pharmacologically with an initial brief increase in the turnover of acetylcholine in the hippocampus. The subsequent reduction of phasic theta-ON cell
discharges and theta field activity may be correlated with a longer lasting reduction of
turnover of acetylcholine in the hippocampus, that was controlled by MS/vDBB GABA-
A inputs to MS/vDBB cholinergic septohippocampal neurons, possibly along with a
direct inhibition of the GABAergic septohippocampal projection; the contribution of the
MS/vDBB nuclei, as the node of the ascending brainstem hippocampal synchronizing
pathways, was in relaying the ascending theta frequency code, the modulation of theta
amplitude and the correlated discharges of hippocampal formation theta-ON cells.
Furthermore, the HPC participation of phasic theta-ON cells in the generation of
hippocampal theta field activity and sharp waves was mediated by separate inputs.
Recent evidence supporting the existence of a third septohippocampal projection has
accumulated, beginning with the knowledge that a population of MS/vDBB neurons
could not be identified with either cholinergic or GABAergic markers and could possibly
be glutamatergic (Kiss, et al., 1997; Gritti et al. 1997). Next, analysis using phosphate-
activated glutaminase and by the retrograde transport of $[^3]$H aspartate in septal neurons
provided indirect evidence for MS/vDBB glutamate neurons (Gonzalo-Ruiz and Morte,
2000; Manns, et al. 2001; Kiss et al. 2002). Two types of vesicular glutamate transporters
have now been well documented in excitatory synapses (VGLUT1 and VGLUT2)
(Fremeau, et al., 2001). Strong evidence for the presence of glutamate neurons in the
MS/vDBB has been provided by single-cell multiplex RT-PCR that has identified a sub-
population of septohippocampal neurons expressing mRNAs for VGLUT1 and VGLUT2
antibody and a retrograde tracing technique to identify a sub-population of
septohippocampal glutamatergic neurons in the medial septal region. Using stereological
probes these authors concluded that in the rat the septohippocampal glutamatergic population comprised approximately 16,000 neurons. In addition, based on triple immunostaining, they provided evidence that most glutamatergic neurons did not immunoreact with cholinergic or GABA-ergic neuronal markers in the medial septum. Previous evidence in the literature suggested glutamate might play a role in HPC theta band oscillation and synchrony. Carre and Harley (2000) demonstrated that the injection of glutamate into the medial septum resulted in the generation of hippocampal theta. Bonansco and Buno, 2003) showed that theta-like rhythmic oscillations of CA1 cell membrane potentials (MPOS) and rhythmic spike discharges could be induced by the microiontophoresis of N-methyl-d-aspartate (NMDA) at the apical dendrites of CA1 pyramidal cells in the in vitro hippocampal slice preparation. Bland, et al. (2006c) recently demonstrated that the microinfusion of NMDA into apical dendrites of hippocampal CA1 pyramidal cells of urethane-anesthetized rats resulted in long lasting (20-30 mins) induction of hippocampal synchrony at the field and cellular level (see Figure 10).
Power of NMDA-induced theta was significantly greater than tail pinch-induced theta activity but frequency did not differ. This effect was antagonized by intrahippocampal infusion of AP5, but unaffected by I.V. ATSO4. During AP5 blockade tail pinch theta
frequency and power were significantly reduced. Microinfusion of NMDA into the medial septum also resulted in the induction of HPC theta field activity significantly higher in frequency than tail pinch-induced theta activity, while power did not differ. Microinfusion of AP5 into the medial septum significantly lowered the power of tail pinch-induced theta but did not affect frequency. These findings supported the conclusion that the glutamatergic septohippocampal projection represents a third pathway capable of generating hippocampal field and cellular synchrony, independent of that generated by the septohippocampal cholinergic and GABA-ergic projections. The possible functional significance of this system will be discussed later.

One of the widely accepted beliefs concerning the role of the medial septal region in hippocampal theta generation is that it serves a “pacemaker” function. Although this is subject to various interpretations, in the strictest sense this implies that the generation of rhythmic activity in the hippocampus is produced as a result of rhythmic inputs from the septum. The acceptance of this notion is easy to understand, given that many medial septal cells discharge in a rhythmic pattern and lesions of the region abolish theta field activity in the HPC. However, Bland and Colom (1993) reviewed evidence supporting their belief that the septal “pacemaker” hypothesis in its strictest interpretation was not tenable. Chief among this evidence was the demonstration that carbachol applied to isolated hippocampal slices resulted in the generation of theta field activity (Konopacki, et al., 1987a, b, c, d; Konopacki, et al., 1988a,b, c; Bland, et al., 1988). Rowntree and Bland (1986) had previously demonstrated that the intrahippocampal microinfusion of carbachol in septally intact urethane-anesthetized rats was capable of generating hippocampal theta field activity. Despite these findings, Colom, et al. (1991) were unable
to induce hippocampal theta in urethane-anesthetized rats following intrahippocampal microinfusions of carbachol, with the medial septum temporarily blocked with procaine hydrochloride. These authors reasoned that this failure could be due to the fact the removal of septal GABAergic inputs in the anesthetized preparations may leave the hippocampus “hyperinhibited”. This did not happen in transverse hippocampal slices since many dendritic arbors of GABA-ergic interneurons ran parallel to the main hippocampal axis and were severed in transverse cuts. Slices thus contained a reduced population of inhibitory interneurons and therefore reduced inhibition. Colom, et al. (1991) demonstrated that the combination of carbachol and bicuculline microinfusions into the HPC of septally deafferented rats produced theta-like field oscillations and rhythmic discharges of phasic theta-ON cells, both of which were antagonized by atropine sulfate (see Figure 11).
If the medial septal region does not serve as a pacemaker what role does it play in hippocampal theta generation? Recent findings support the view that hippocampal theta field frequency is primarily determined by brainstem nuclei below the medial septum (the
pontine and diencephalic nuclei) while the medial septum relays frequency information and contributes primarily to theta amplitude (Kirk and MacNaughton, 1993; Bland and Oddie, 2001; Pan and MacNaughton, 2004; Woodnorth and MacNaughton, 2005; Jackson and Bland, 2006; Bland, et al. 2006a). Jackson and Bland (2006) used independent and combined electrical stimulation pairings of the pontine nucleus, posterior hypothalamus and medial septum in urethane anesthetized rats to determine the contribution of the septum to the frequency and amplitude parameters of HPC theta generation. Their findings supported several conclusions: (1) the major theta generating activity of the ascending brainstem hippocampal synchronizing pathways involved projections from the pontine region to the posterior diencephalic region, relayed through the medial septal region to the hippocampus; (2) the medial septal region directly controlled theta amplitude and secondarily translated the level of ascending brainstem activity into the appropriate frequency of HPC theta.

Another long-standing paradox in the theta literature concerned the effects of electrical stimulation of the medial septal region. Electrical stimulation of the medial septum of urethane anesthetized rats at appropriate parameters produced hippocampal theta field activity (Bruke, et al., 1959; Stumpf, 1965; Gray and Ball, 1970). Similar stimulation of the medial septal in freely moving rats also produced theta, but it was dissociated from the normal behavior correlates (Kramis and Routenberg, 1977), in direct contrast to the effects of posterior hypothalamic stimulation (Bland and Vanderwolf, 1972a; Oddie, et al. 1996). A paper by Scarlett, et al. (2004) provided a possible explanation for the dissociation between the induced hippocampal theta field activity and its behavioral correlates. These authors showed that theta induced by electrical stimulation of the
septum indeed had the same depth profile as spontaneously occurring theta. However, the responses of theta-related cells to medial septal stimulation were very different from the discharge properties of these cells in relation to spontaneously occurring theta, and to those accompanying electrical stimulation of the pons and posterior hypothalamic region. Thus, on the basis of cellular evidence, electrical stimulation of the medial septum activated hippocampal neural circuitry involved in the generation of theta field activity in a nonphysiological manner that is, in addition, devoid of behaviorally relevant sensorimotor inputs from the posterior hypothalamic region.

The fact that lesions of the medial septal region abolished theta field activity was discussed above. Smythe et al. (1991), also showed that reversible blockade of the MS/vDBB nuclei with procaine abolished spontaneously occurring HPC theta and HPC theta produced by electrical stimulation of the PH. In addition, they demonstrated that the blockade abolished the rhythmic discharges of HPC phasic theta-ON cells and caused the release (disinhibition) of the discharges of phasic theta-OFF cells. During the period of the blockade when the discharges of phasic theta-OFF cells were released, electrical stimulation of the PH was no longer effective in inhibiting these discharges. The study thus confirmed that the medial septal region mediated the synchronizing influences of PH stimulation on HPC field and phasic theta-ON cell activity, as well as the inhibition of phasic theta-OFF cells.

Simultaneous recordings of septohippocampal cells have provided more information concerning the critical role of the medial septum in the control of oscillation and synchrony in the HPC. Macadar et al. (1970) and Alonso et al. (1987) were the first to do such studies, utilizing time-averaged cross-correlation techniques. Bland et al.
(1997,1999) subsequently carried out experiments utilizing urethane-anesthetized rats in which 18 simultaneously recorded septohippocampal cell pairs (36 individual cells), each classified as theta-related according to the criteria of Colom and Bland (1987), were studied during four spontaneously occurring HPC field conditions: (1) large amplitude irregular activity (LIA) only; (2) the transition from LIA to theta; (3) theta only, and (4) the transition from theta to LIA. The main objective was to examine the temporal relationships and degree of neural synchrony between the discharges of cell pairs during the four conditions, utilizing both time-averaged and time-dependent (Joint Perstimulus Time Histogram Analysis, JPSTH) cross-correlation techniques, in order to determine their contribution to the control of oscillation and synchrony (theta) in the HPC. The JPSTH analysis, which assessed the time-dependent correlation between the spontaneous discharges of two cells, has generally been interpreted as indications of their interconnectivity and/or the sharing of a common input (Gerstein, 1970). The findings of Bland, Oddie, and Colom (1999) demonstrated that the transition from the LIA state to the theta field state in the HPC required a temporal sequence of changes in theta-related cellular activity occurring an average of 500 msec preceding the transition, which were suggested to be: (1) the medial septum inhibited HPC theta-OFF cells; (2) tonic MS/vDBB theta-ON cells provided tonic depolarizing inputs to initiate MPOs in HPC phasic theta-ON cells, whereas phasic MS/vDBB theta-ON cells synchronized the MPOs of phasic HPC theta-ON cells and the discharges of tonic HPC theta-ON cells. Much of the time preceding the LIA to theta field transition was accounted for by recruitment of these theta-related cell populations. On the other hand, the “turning off” of the theta state
occurred abruptly and involved the medial septal activation of hippocampal theta-OFF cells.
The “turning off” of the theta state, that is, the initiation of hippocampal desynchronization, is mediated by another group of ascending brainstem pathways that originate in the nucleus of the median raphe. The ascending brainstem hippocampal synchronizing and desynchronizing systems are likely to interact at a number of levels, with the medial septal region as the “node” for both systems. Bland and Vanderwolf (1972b) may have activated the terminal portions of the desynchronizing system in their early study. They demonstrated that electrical stimulation of sites in the dentate-CA4 region of the HPC produced short latency evoked potentials bilaterally in the HPC that supplanted the normal theta field activity and resulted in the immediate behavioral arrest of Type 1 movements. This same stimulation did not interfere with ongoing Type 2 behaviors such as conditioned immobility, shivering or licking. In this same series of experiments, Type 1 movement related theta was recorded from the posterior hypothalamus and electrical stimulation of the dentate-CA4 region supplanted this activity as well. The raphe system will be discussed in the following section.

The ascending brainstem hippocampal desynchronizing pathways

The median raphe

The median raphe nucleus (MR) is a serotonin-containing cell group located in the midbrain, sending projections to many forebrain regions (see review by Vertes, et al., 2004). Among these are very strong projections to the medial septal region as well as direct connections to the HPC and SUM regions (Aznar, et al., 2004; Vertes, et al., 1999). One of the earliest documented findings was the demonstration that electrical stimulation
of the MR resulted in desynchronization of hippocampal field activity (Assaf and Miller, 1978; Macadar, et al., 1974, Vertes, 1981) while lesions of the MR resulted in the continuous release of theta (Maru, et al., 1979; Yamamoto, et al., 1979). These effects are likely to be mediated by serotonergic cells in the MR since injections of drugs that either suppressed serotonergic neurons in the MR of anesthetized rats (5-HT₁A autoreceptor agonists or GABA agonists) or reduced excitatory drive to them (excitatory amino acid antagonists) produced long-lasting theta field activity (Kinney, et al., 1994, 1995, 1996; Vertes, et al. 1994). Varga, et al. (2002) reported that GABA_B receptors are found on serotonergic MR cells and that there activation by the agonist baclofen also resulted in long-lasting theta generation. The MR also contains a population of GABAergic cells that likely inhibit serotonergic MR cells (see review by Vertes, et al., 2004). Viani Di Prisco, et al. (2002) demonstrated that approximately 80% of MR cells could be categorized as theta-ON or theta-OFF cells and further related their discharge properties to putative serotonergic or GABAergic cells.

Electrical stimulation of the MR in anesthetized rats also has a disruptive effect on rhythmically discharging medial septal neurons (Assaf and Miller, 1978) while in freely moving rabbits such stimulation also disrupted the rhythmic discharges of both medial septal cells and hippocampal theta (Kitchigina, at al., 1999; Vinogradova, et al. 1999). These authors also reported that the suppression of the MR by lidocaine increased the frequency and regularity of rhythmically discharging cells in the medial septum and hippocampus as well as producing continuous hippocampal theta field activity. A study by Segal (1975) demonstrated that electrical stimulation of the MR resulted in the inhibition of 48% of recorded hippocampal pyramidal cells, although in this study the
cells were not rigorously characterized according to theta-related properties. Recent work in our lab has shown that electrical stimulation of the MR in urethane anesthetized rats that suppressed ongoing theta also resulted in a short latency inhibition of 100% of all phasic theta-ON cells tested (Jackson, et al., 2006). The effects of electrical stimulation of the MR on hippocampal field and cellular activity may be mediated by a number of different pathways, either direct or indirect. Given the data discussed above that such stimulation affects medial septal cell activity, a route through the septum is suggestive but not proven. A seemingly obvious test in anesthetized rats would be to procaine the septum to see if the effects of MR stimulation (abolishing theta) would be disrupted. However, this manipulation itself abolishes theta. Crooks, et al., (unpublished data) solved this problem by looking at the effects of procaine suppression of the medial septum on the release of theta produced by either procaine injections or injections of 8 – OHDPAT in the MR. The experiments revealed that procaine injections into the medial septum abolished the released theta, thus supporting the view that the effect of electrical stimulation of the MR on the hippocampus was modulated by pathways through the septum.

The sensorimotor integration model would predict that MR stimulation in the freely moving rat should result in the inhibition of Type 1 theta-related behaviors. Several earlier studies could be interpreted as support for this prediction (although the authors had different interpretations). Graeff and Silveira Filho (1978) and Graeff, et al. (1980) reported seeing behavioral inhibition or behavioral “freezing” as a result of MR stimulation in freely moving rats. Robinson and Vanderwolf (1978) demonstrated that MR stimulation at a frequency of 100 Hz resulted in the generation of slow 4 – 6 Hz theta
and transient behavioral arrest. Peck and Vanderwolf (1991) showed that stimulation of some sites in the MR of freely moving rats induced theta and locomotion while stimulation of most sites in the MR resulted in behavioral freezing and theta. Treatment with scopolamine abolished the theta, replacing it with hippocampal suppression, while not affecting the behavioral suppression. Jackson, et al. (2006b) carried out a study investigating the effects of MR stimulation on wheel running and hippocampal theta field activity induced by posterior hypothalamic stimulation. Electrical stimulation of the MR resulted in the total inhibition of wheel running, accompanied by slow frequency theta, even during the continued application of posterior hypothalamic stimulation. When the MR stimulation was turned off, the rat immediately resumed intense wheel running accompanied by higher frequency theta. These data thus support the hypothesis that the functional significance of the MR HPC desynchronizing system is to terminate Type 1 theta related movements.

**The motor feedback role of the posterior hypothalamic region**

As discussed earlier, significant additions to the updated sensorimotor model included the description of the ascending brainstem hippocampal synchronizing pathways as the anatomical basis of the model, with the posterior hypothalamic region assigned the role of providing motor feedback to the hippocampal formation. In the updated version, Type 2 theta inputs ascended from the pontine region to the midline diencephalic region, through to the medial septum and then input to the hippocampus. In the case where Type 1 movements were not yet been initiated, the hippocampus sent only Type 2 inputs to motor systems. Initiation of Type 1 movements by motor systems sent Type 2 and Type 1
inputs to the posterior hypothalamus that again ascended through their respective pathways to the medial septum and to the hippocampus. Experiments investigating the effects of electrical stimulation of nuclei contributing to the ascending brainstem hippocampal synchronizing pathways on hippocampal field activity and behavior of freely moving rats provided strong support for these ideas. Robinson and Vanderwolf (1978) showed that stimulation of many brainstem sites (nucleus cuneiformis; subnucleus compactus; nucleus reticularis oralis, caudalis, and medial gigantocellularis; the pontine central gray; nuclei adjacent to the midbrain central gray; centralis superior of the raphe; locus coeruleus) at lower levels of intensity produced Type 2 (atropine-sensitive) theta during behavioral immobility. At slightly higher levels of stimulation of most sites walking or circling behavior occurred, accompanied by Type 1 (atropine-resistant) theta. Similar studies of the posterior hypothalamic region have revealed that this area differs from other brainstem sites in that the Type 1 movements elicited were under environmental control. Bland and Vanderwolf (1972a) demonstrated that rats receiving electrical stimulation of the posterior hypothalamus could turn to avoid obstacles and reversed direction when necessary and speed of locomotion was increased as stimulation intensity increased. Type 2 behaviors never occurred during the periods of electrical stimulation. Theta frequency was related systematically to the speed of initiation of Type 1 movements. In a running wheel experiment, the speed of initiation of running was directly related to the level of posterior hypothalamic stimulation and the onset frequency of HPC theta. These experiments did not prove that the theta and movements induced by electrical stimulation of the posterior hypothalamus were both dependent on activity ascending to the hippocampus. Later experiments did provide support for this being the
case. Oddie, et al (1996) replicated and extended Bland and Vanderwolf’s (1972a) wheel running results by adding in the manipulation of septo-hippocampal pathways. Following the baseline condition the medial septal region was reversibly inactivated by the microinfusion of procaine hydrochloride. The stimulation induced wheel running and HPC theta were both abolished. Subsequent multiple regression analysis revealed that the recovery of wheel running speeds more closely paralleled the recovery of HPC theta frequency rather than HPC theta amplitude.

Experiments carried out in Sinnamon’s lab have also provided important data supporting the relationship between hypothalamic sites and locomotor behavior. Utilizing a paradigm involving lightly anesthetized rats suspended in a sling, he demonstrated that electrical stimulation of hypothalamic nuclei induced locomotor stepping (Sinnamon (1993). He has also demonstrated that the locomotor stepping induced by electrical stimulation of these hypothalamic nuclei was accompanied by HPC theta, albeit at lower frequencies than in the awake rat (Sinnamon, Jassen and Ilch, 2000). A subsequent study (Sinnamon, 2000) demonstrated that the association between HPC theta activity in the 3-6 Hz range and the excitability of locomotor initiation was sufficiently specific to allow prediction of the magnitude of stepping by the prior power levels of HPC 3-6 Hz theta.

The experiments discussed above demonstrated that activation of the posterior hypothalamus induced Type 1 motor behaviors correlated with Type 1 theta. Destruction of this area should profoundly affect motor behavior and theta and indeed this was the case. Robinson and Whishaw (1974) showed that large lesions of the posterior hypothalamus produced profound akinesia together with the loss of type 1 movement related theta.
Data supporting the sensorimotor integration model of hippocampal function

The sensorimotor integration model was based on the assumption there were at least two separate theta inputs to the HPC, one for generating Type 1 movement related theta and one for generating Type 2 sensory processing theta, and that the Type 2 theta subsystem was always coincidently active whenever the Type 1 theta subsystem was active. Early support for the “two theta’s” concept came from the observations that immobility related Type 2 theta was atropine sensitive while movement related Type 1 theta was atropine resistant (Bland, 1986) and the demonstration by Leung (1984a) that the gradual phase shift of theta observed in depth profiles made through the CA1 stratum radiatum of the HPC of freely moving rats was related to the relative participation of the Type 2 and Type 1 theta generating pathways. Activation of the Type 2 pathway by itself resulted in the rapid $180^\circ$ phase shift observed in urethane-anesthetized rats. Addition of Type 1 theta during the occurrence of Type 2 theta resulted in a gradual phase shift. In a subsequent paper Leung (1984b) provided a model of the CA1 pyramidal region that successfully explained the type of theta profiles one would expect to see under various experimental conditions, including providing support for the idea that Type 1 and Type 2 theta inputs were both active during Type 1 movements. Sinclair, et al. (1982) demonstrated that phasic theta-ON cells (simply termed theta cells at that time) discharged in rhythmic bursts during both Type 2 immobility related theta and Type 1 movement theta (see Figure 12).
Interestingly, the number of discharges per rhythmic burst was always lower during Type 2 theta compared to Type 1 theta, even when the theta field frequencies accompanying the two behaviors were identical. This provided physiological evidence there was a
difference in inputs to the same cell during sensory processing and movement. Furthermore, although not investigated systematically, the study provided evidence that the higher the theta field frequency, the greater the number of discharges per burst. This relationship was investigated in detail in a subsequent study (Bland, et al, 1983), and shown to hold for both Type 2 and Type 1 theta conditions. These observations supported the idea that individual theta-ON cells coded for increasing levels of activation of sensory inputs and increasing levels of activation (speed of initiation) of movements. In a subsequent study Bland, et al (1984) administered atropine sulfate to rabbits during the presentation of sensory stimuli while immobile. As predicted, both Type 2 theta and the theta-ON cell rhythmic discharges were abolished by the administration of atropine sulfate but continued to discharge in a rhythmically bursting pattern during the Type 1 theta accompanying movement. However, the number of discharges per rhythmic burst was reduced compared to the pre-atropine condition (see Figure 12).

Recent work by Shin et al. (2005) has provided additional strong support for the presence of both atropine sensitive and atropine resistant theta using a genetic knockout model. The PLC-β-1- isoenzyme is the most critical of the four identified PLC-β isoenzymes in studies of hippocampal theta rhythms as it is coupled to muscarinic receptors (Kim et al., 1997) and Group 1 mGluRs in the hippocampus (Chuang et al., 2001). Knockout mice for the PLC-β-1- gene were shown to lack atropine-sensitive (Type 2) theta while atropine-resistant (Type 1) theta was intact. Carbachol-induced theta oscillations were abolished in hippocampal slices from PLC-β-1- knockout mice, and in urethane-anesthetized PLC-β-1- knockout mice Type 2 theta was absent. In freely moving PLC-β-1-
knockout mice, theta was preserved during Type 1 theta-related behaviors such as walking and running.

As discussed earlier, there is strong evidence for a septohippocampal glutamatergic pathway and support for it being involved in theta generation. Leung and Desborough (1988) previously reported that the infusion of AP5 into the lateral ventricles of freely moving rats resulted in the attenuation of HPC theta rhythm and the theta phase shift at the apical dendrites in the CA1 region. These authors suggested that this effect was a selective suppression of Type 2 (atropine-sensitive) theta. Leung and Shen (2004) carried out a study to test whether the effects of the intraventricular AP5 administration they reported earlier were due to its action on the septum or HPC. They showed that AP5 infusions directly into either the HPC or the medial septum reduced the power but not the frequency of HPC theta. What might be the functional significance of this third theta-generating pathway? Bland, et al. (2006) showed that wheel running behavior of rats induced by low levels of electrical stimulation of the posterior hypothalamic nucleus was completely abolished by microinfusion of the NMDA antagonist AP5 into the medial septum, accompanied by a significant reduction in theta amplitude (power). Wheel running and theta were maintained at control levels in a high level PH stimulation condition. Bland, et al. (2006c) hypothesized that the glutamatergic septohippocampal projection provided the excitatory drive for the rapid initiation of movement, superimposed on the tonic cholinergic/GABA-ergic drive occurring during the sensory processing period prior to movement. A study by Bland, et al. (2006b) provided some insight as to how this might work. In these experiments rats were trained in an avoidance task to jump out of a box, the distance of which could be varied at 3 different heights.
Amplitude and frequency of HPC Type 2 theta was measured in the immobility period just prior to jump initiation. The same parameters were measured for the Type 1 theta “jump” wave as well as measurements of the phase of the jump wave in relation to the moment of jump initiation. The results demonstrated that the immobility period prior to the execution of the jump could be divided into two components: a sensory processing period and a movement preparation period (see Figure 13).
Comparing these two periods, average amplitudes were higher while frequency remained relatively constant during the sensory processing period. During the movement preparation period there was a negative correlation between amplitude and frequency:
amplitude declined rapidly and frequency increased rapidly. During the execution of the jump, theta (Type 1) amplitude and frequency were positively correlated, both reaching peak values. Both the amplitude and the frequency of the Type 1 theta jump wave increased as jump height increased. These results supported the hypotheses that Type 1 theta amplitude was associated with the magnitude of the movement and Type 1 theta frequency was associated with the speed of initiation of the movement. A significant phase preference was demonstrated for the highest jump height, with movement initiation occurring around the trough of theta recorded from the stratum moleculare of the dentate region. These data suggested that Type 2 theta amplitude (power) during the sensory processing period might be associated with the determination of movement initiation while the frequency of Type 2 theta during the movement preparation period was associated with the intensity of initiation of that movement. In the wheel running experiment discussed above, the microinfusion of AP5 into the medial septum resulted in the reduced amplitude of theta and blocking of PH-induced wheel running at lower levels of PH stimulation. Increasing the level of PH stimulation resulted in an increase in theta amplitude, and running occurred.

Bland, et al. (unpublished results) recently carried out another set of experiments designed to determine if there was a relationship between Type 2 theta and subsequent movement. One group of rats were trained to escape shock in a runway avoidance task while another group received the same number and intensity of shocks but could not escape the start box. Twenty-four hours later both groups received a single shock probe in an open field test box. Most rats responded to the shock probe with “freezing” behavior (immobility). Rats trained to avoid generated Type 2 theta during immobility,
while rats that could not escape produced LIA during the immobility period. Similar results were first reported by Balleine and Curthoys (1991). Our interpretation of these results was that rats receiving inescapable shock learned that the shock was not associated with the possibility of movement, and thus in the probe test produced only LIA, contrary to the avoidance trained rats. To test this hypothesis the rats received reversal training: the avoidance group received inescapable shock while the inescapable group was trained to avoid. The avoidance group retrained with inescapable shock now produced LIA in the shock probe test while the inescapable group retrained in avoidance produced Type 2 theta, thus supporting the hypothesis that previous experience determined whether movement preparation would occur.

Several other studies have carefully examined changes in hippocampal theta related to sensorimotor behavior (see review by Oddie and Bland, 1998). Oddie, et al. (1997) tested the idea that Type 2 theta played a role in sensory integration and the neural processing required for the initiation of Type 1 movements, using a behavioral paradigm called “ducking and robbing”. One of a pair of hungry rats, the victim, was given food that the other rat, the robber, would attempt to steal. Because the victim dodged from the robber with a latency, distance and velocity dependent on the size of the food, elapsed eating time and proximity to the robber, the movement required sensory integration and planning of subsequent movements. The study showed that although eating behavior continued and Type 1 theta was still recorded during movement, the intraseptal microinfusion of atropine sulfate abolished Type 2 theta and dodging behavior was severely disrupted. Wyble et al. (2004) reported a decrease in theta power in a runway task when rats were to receive reward following voluntary movement, and no decrease
when the task went unrewarded. Both amplitude and frequency of theta have been shown to decrease as rats are completing a locomotor approach sequence (Sinnamon, 2005a). Sinnamon (2005b) also identified changes in the time course of maximal frequency and amplitude of hippocampal theta. This study identified a dissociation between frequency and amplitude as rats prepared to initiate or inhibit locomotion toward the possible presentation of a food pellet. Specifically, amplitude increased before the food pellet was presented, indicating that the rat was preparing to process the upcoming sensory information, and frequency increased in the moments before movement during certain trials. During consumatory behaviors (such as milk lapping and consumption of food rewards) theta amplitude is reported to decrease in power, likely due to the automatic nature of the behavior (Wyble et al., 2004; Sinnamon, 2005b). Similarly, van Lier et al. (2003) demonstrated that during behavioral transitions, amplitude increased following a Type 1 behavior (voluntary movement) and was reduced when following an automatic, Type 2 behavior.

Much of the work discussed in the context of the sensorimotor integration model has dealt with how ascending sensory information is processed by the hippocampus. The model predicts that there would be relationships between the neural activity underlying theta band oscillation and synchrony in the hippocampal formation (and related structures) and the neural activity in motor structures. Examinations of these possible relationships between the hippocampus, deep layers of the superior colliculus, the basal ganglia and the red nucleus have indeed provided support for this hypothesis (Natsume, et al. 1999; Hallworth and Bland, 2004; Dypvik and Bland, 2004).
Since the data discussed above is based on animal research a fair question to ask is the sensorimotor integration model of hippocampal function relevant to humans? A long-standing controversy in the literature revolved around the question of whether theta band oscillation and synchrony could even be recorded from the hippocampus of primates and man. The answer is yes it can and it appears to be related to sensorimotor integration (Caplan, et al., 2004, Ekstrom, et al., 2004).

Figure 14 presents a diagrammatic representation of the anatomical basis of the model, including the ascending brainstem hippocampal synchronizing pathways as the basis of initiating sensorimotor integration and the ascending brainstem desynchronizing pathways as the basis of terminating sensorimotor integration. The connectivity is oversimplified for clarity.
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Figure Legends

Figure 1. A. Relationship between spontaneously occurring hippocampal theta field activity and discharges of a CA1 pyramidal cell. Top: the hippocampal field activity recorded dorsal to the CA1 pyramidal cell layer in stratum oriens, bottom: the discharge pattern of a CA1 pyramidal cell (256) classified as a phasic theta-ON cell (positivity up in all traces). The cell discharged in a rhythmic pattern with 4 – 5 spikes riding on the positive phase of the MPOs and the negative phase of the locally recorded extracellular theta field. B. Relationship of the same cell to spontaneously occurring hippocampal LIA field activity. Note the overall lower discharge rate, irregular discharge pattern and lack of MPOs. C. Current-voltage plot of cell 256, input resistance = 29 MΩ. Low power photomicrograph insert shows the location of the cell in the CA1 pyramidal layer while the higher power magnification insert confirmed its identity as a CA1 pyramidal cell. Calibration bar = 50 μ. Reprinted with permission from Elsevier Science Publishers B.V.

Figure 2. A and B. Relationships between spontaneously occurring HPC field activity and the spike discharges of a CA1 layer basket cell (# 229) classified as a phasic theta-OFF cell, in the no current control condition. The upper trace in each panel is the HPC field activity recorded from the molecular layer of the dentate region and the lower trace is the discharge pattern of the cell. The first half of the panels in A and B show the irregular cell discharge pattern occurring during HPC LIA. Note the absence of MPOs. The second half of the panel in (A) shows the complete cessation of spike discharges during theta field activity with at a higher frequency (4.3 Hz) and the occurrence of MPOs. The second half of the panel in (B) shows that as theta field frequency slowed to 3.4 Hz, phase-locked spike discharges began to occur. Again, MPOs were recorded during theta field activity. C. Intracellular depolarizing current pulse (200 pA, 100 msec duration) applied to the cell during spontaneously occurring theta. D. The intracellular injection of Neurobiotin™ into cell # 229 resulted in the labeling of a cell identified as a CA1 pyramidal layer basket cell. The upper panel is a low power magnification showing the location of the cell in the CA1 cell pyramidal layer. The lower panel is a higher power magnification showing the details of cell morphology. Calibration bar = 50 μ. E. Current- voltage plot of the cell shown in Figure 1A, input resistance = 29.4 MΩ. Reprinted with permission from the American Physiological Society.

Figure 3. Sample recordings of an MS/vDBB phasic theta-on cell that was rhythmic during HPC LIA, during the conditions of HPC theta (upper panels), spontaneous LIA (middle panels), and microinfusion of procaine hydrochloride into the PH (lower panels). Post-procaine data collected between 1 and 10 min after infusion of procaine. Reprinted with permission from John Wiley and Sons, Inc.

Figure 4. Responses of a dentate area theta-on cell to a tail pinch, spontaneous LIA, and a tail pinch post-atropine (upper panels), increasing levels of PH stimulation (middle panels), and increasing levels of PH stimulation post-atropine (lower panels). Reprinted with permission from Elsevier Science Publishers B.V.
**Figure 5.** Responses of a CA1 area theta-off cell following PH stimulation. Note this type of cell was silent during slow wave frequencies above 5 Hz (first second post-stimulation). Reprinted with permission from Elsevier Science Publishers B.V.

**Figure 6.** The relation between the discharge patterns of a phasic linear theta-OFF cell in the dentate granule layer and the simultaneously recorded field activity from the dentate stratum moleculare. A: spontaneous LIA and hypothalamic stimulation (500 microamps) during control conditions and B: spontaneous activity and hypothalamic stimulation (500 microamps) following the administration of atropine sulfate. Reprinted with permission from Elsevier Science Publishers B.V.

**Figure 7.** Discharge patterns of representative CM (left) and PH (right) tonic theta-ON cells during spontaneously occurring hippocampal theta and large-amplitude irregular activity (top). Bottom: digitized coronal sections through the caudal diencephalon. Arrows: locations of the pontamine sky blue dot deposited from the tips of the glass microelectrodes used to record the cells shown above. Tonic theta-ON cells were located predominately in the CM and PH. Reprinted with permission from the American Physiological Society.

**Figure 8.** Discharge patterns of a nonrelated cell in the PH (left) and a tonic theta-cell in the PH/SUM border region (right) during spontaneously occurring hippocampal theta and LIA (top). Bottom: digitized coronal sections through the caudal diencephalon. Arrows: locations of the pontamine sky blue dot deposited from the tips of the glass microelectrodes used to record the cells shown above. Nonrelated cells were found throughout the caudal diencephalon, whereas tonic theta-OFF cells were found predominately in the PH/SUM border region. Reprinted with permission from the American Physiological Society.

**Figure 9.** Discharge patterns of representative SUM (left) and MM (right) phasic theta-ON cells during spontaneously occurring hippocampal theta and LIA (top). digitized coronal sections through the caudal diencephalon. Arrows: locations of the pontamine sky blue dot deposited from the tips of the glass microelectrodes used to record the cells shown above. Phasic theta-ON cells were located predominately in the SUM and the MM. Reprinted with permission from the American Physiological Society.

**Figure 10.** A. Time-frequency contour plot (red = high power, blue = lowest power) and Fast-Fourier (FFT) analyses of hippocampal field activity during various experimental conditions: Time-frequency analysis in upper panel shows the sequence of a control tail pinch, followed by NMDA microinfusion into the HPC (first arrow), and then the administration of ATSO4 (second arrow). Lower left FFT is a control tail pinch (first asterisk), middle FFT is a sample of NMDA-induced theta (second asterisk), and right side FFT is a sample of theta field activity at the peak frequency following the I.V. administration of ATSO4. Note that the lack of effect of ATSO4 on the power of NMDA-induced theta field oscillations. B. Time-frequency contour plot (red = high power, blue = lowest power) and Fast-Fourier (FFT) analyses of hippocampal field activity during various experimental conditions: Time-spectral analysis in upper panel
shows the sequence of a control tail pinch, followed by NMDA microinfusion into the HPC (first arrow), and then the microinfusion of AP5 into the HPC (second arrow). Lower left FFT is a control tail pinch (first asterisk), middle FFT is a sample of NMDA-induced theta (second asterisk), and right side FFT is a sample of theta field activity at the peak frequency following the microinfusion of AP5 into the HPC. Note that the NMDA-induced theta field oscillations were abolished by AP5 and that the power of the primarily cholinergically mediated tail pinch theta field activity was reduced compared to that produced before the AP5 treatment. Reprinted with permission from John Wiley and Sons, Inc.

**Figure 11.** The effects of intrahippocampal microinfusions of carbachol plus bicuculline on field activity and theta-ON cell discharges. Analogues are the simultaneously recorded field and cellular activity from the dentate molecular layer (upper trace) and a phasic theta-ON cell in the CA1 layer (lower trace) during various pre- and postprocaine conditions. Reprinted with permission from John Wiley and Sons, Inc.

Figure 12. Relationships between the discharge patterns of a dentate area theta-ON cell to hippocampal field activity recorded from the stratum molecular layer recorded from a freely moving rabbit. A. Pre-drug condition. Recordings taken during hopping (top panel), immobility during a tone presentation (middle panel), and during immobility (bottom panel). B. Post-atropine administration. Recordings taken during hopping (top panel), immobility during a tone presentation (middle panel), and during immobility (bottom panel). Reprinted with permission from Elsevier Science Publishers B.V.

**Figure 13.** A: Graph of group data collapsed across the three jump heights showing the progression of theta frequency before, during, and after the jumps. Each data point is the grand mean ± standard error derived from the averages of 30 measurements for each of the seven animals. Note the steep increase in frequency during the movement preparation period before the jump, and including the jump wave. Frequency declined beginning with the first post jump wave. B: Graph of group data collapsed across the three jump heights showing the progression of theta amplitude before, during, and after the jumps. Each data point is the grand mean ± standard error derived from the averages of 30 measurements for each of the seven animals. Amplitudes for each animal were normalized before averaging. Note the increase in amplitude during the sensory processing period and for the jump wave. Amplitude continued to increase up to the first post jump wave jump wave and subsequently declined. Reprinted with permission from John Wiley and Sons, Inc.

**Figure 14.** An updated diagrammatic representation of the sensorimotor model for the hippocampal formation theta subsystems. Ascending hippocampal synchronizing Type 2 sensory processing inputs on illustrate that Type 2 theta can occur in isolation. Once a
Type 1 (voluntary) movement is initiated, there is always a co-activation of Type 1 and Type 2 inputs, as illustrated by the addition Type 1 movement inputs from motor regions. The main median raphe ascending hippocampal desynchronizing input is also mediated by the medial septum. Reprinted with permission from Elsevier Science Publishers B.V.