THE ROLE OF THETA-RANGE OSCILLATIONS IN SYNCHRONISING AND INTEGRATING ACTIVITY IN DISTRIBUTED MNEMONIC NETWORKS

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ABSTRACT

It is well established that the occurrence of theta rhythm in the hippocampus is important in a variety of mnemonic tasks. However, in this review it will be argued that theta-rhythmic activity occurs across distributed networks within the diencephalon and neocortex as well as the hippocampus, and functions to temporally coordinate activity in distributed systems within these regions during mnemonic processes. Recent evidence strongly suggests that theta-range cellular activity occurs in the supramammillary nucleus (SuM) of the hypothalamus, and that this activity is independent of that occurring in the hippocampus. We have previously proposed in fact, that the frequency of theta activity in the hippocampus is determined in the SuM, rather than in the medial septum as previously assumed. The frequency-coded information from the SuM is then fed into at least two recurrent networks proposed by Aggleton and Brown (1999). Theta activity in these networks (the hippocampo-anterior thalamic system and the perirhinal-mediodorsal thalamic system) could potentially occur independently, but when simultaneously occurring in both may function to coordinate the integration of information in the two systems. Finally, we suggest that as the two systems include temporal and frontal neocortical areas that contribute to surface EEG, scalp recording of theta EEG activity from these regions may provide a "window" through which to assess the relative involvement of different cortico-limbic circuits in different mnemonic processes. The potential utility of this technique will be increased greatly by the use of high-density EEG and algorithms to more precisely map the topography of cortical sources of EEG activity.

Key words: memory, theta, human EEG, hippocampus, thalamus, hypothalamus

INTRODUCTION

It is widely accepted that mammalian memory in general is mediated by assemblies of interconnected neural networks distributed in nodes throughout the brain. Evidence is also accumulating that different elements in these distributed networks contribute differentially to mnemonic processes (see for example, Aggleton and Brown, 1999; Foster, 1999; Markowitsch, 1999). A critical requirement of a distributed system of this sort is the ability to coordinate activity in the many different parts of the system. It has been proposed that rhythmic slow-wave electrical activity, in the theta range for instance, is a likely mechanism for integration of remote processes (see e.g. Nunez, 1995; Miller, 1991; Kirk, 1998; Klimesch, 1999; von Stein and Sarnthein, 2000 for reviews).

It is well established that theta-rhythmic activity in the hippocampus of experimental animals is critical in a variety of mnemonic processes. Theta (or

theta-frequency cellular activity) has been recorded from, and is probably independently generated, in all subfields of the hippocampus and in the entorhinal and subicular cortices. However, theta generation in both the hippocampus and parahippocampal regions is dependent on phasic input from the medial septum (see Bland, 1986 and Stewart and Fox, 1990 for reviews). Lesions of, or procaine infusion into, the medial septum or fornix superior (afferent drive from, or through which is essential for hippocampal theta) has been repeatedly demonstrated to disrupt performance on mnemonic tasks (see O'Keefe and Nadel, 1978; Bland, 1986; Miller, 1991; Kirk, 1998; Gray and McNaughton, 2000, for reviews). Further, the frequency at which hippocampal theta occurs is regarded as critical for proper functioning of the hippocampal formation in these tasks (Vanderwolf et al., 1975; Klemm, 1976; Gray 1982; Bland 1986; Miller, 1991). For example, McNaughton and Morris (1987) found that systemic injection of an anxiolytic that reduces hippocampal theta frequency impairs performance in a spatial memory task (see Gray and McNaughton, 2000 for extensive review).

In general, representation of information in spatially organized neural networks requires temporal cooperation of elements within the network (Buzsaki and Chrobak, 1995; Gray, 1994; Singer, 1994). This cooperation may be achieved by rhythmic oscillations (such as theta) within a network (such as the hippocampus). Buzsáki and Chrobak (1995) propose that in the hippocampus, theta-rhythmic discharge of a network of inhibitory interneurons impose coordinated inhibitory oscillations on populations of principal cells. In such a scheme, information is represented by temporally contingent or phase-locked discharge of a sub-population of an otherwise intermittently firing principal cell population. In support of this position Buzsáki (1996) suggests that during hippocampal theta activity the majority of principal cells (dentate granule and pyramidal cells) probably discharge at relatively low rates compared to those cells representing for instance, the animal's current spatial location (O'Keefe and Recce, 1993). In addition, it has been suggested that the strength of individual input variables may be represented by the time (or phase) relative to oscillation in the network at which cells discharge (Hopfield, 1995). Recent work showing that the phase (relative to theta) of discharge of place cells advances as the animal passes through a spatial field (phase precession) is consistent with these hypotheses (Jung and McNaughton, 1993; O'Keefe and Recce, 1993; Skaggs and McNaughton, 1996).

The above considerations of the role of theta rhythm in facilitating temporal cooperation amongst elements of a network are usually applied specifically to information flow through the hippocampus, and to and from its immediate efferent and afferent structures. One exception, is the work of Miller (1989, 1991) who proposes that there are differential conduction delays in reafferent loops between the hippocampus and a variety of neocortical loci. Different frequencies of theta enable the hippocampus to preferentially select, and entrain into resonant loops, these different neocortical loci. Correlated or phase locked activity may then result in strengthening of synapses in the selected loop by a Hebbian mechanism.

However, our recent animal work suggests that Miller's general hypothesis regarding the role of theta in hippocampo-cortical integration may be extended to include participation by hypothalamic and thalamic nuclei. Specifically, we

argue that theta-modulated processing in the hippocampus may be integrated with theta activity in the frontal and temporal lobes of the neocortex via a series of recurrent loops involving the hippocampus itself, the mammillary bodies, and projections from the anterior thalamic nucleus to frontal (and/or cingulate) and temporal cortices (Kirk et al., 1997; see Kirk, 1998 for review). All of the above structures have been implicated in mnemonic processes (see e.g. Aggleton and Brown, 1999, for review). We will further suggest that it is possible that non-invasive neocortical recording of theta EEG activity from the scalp in humans may provide a "window" through which to gauge the integrity of limbic theta-related processing. Thus, although activity from the hippocampus itself cannot be directly recorded from scalp electrodes, theta activity recorded over neocortical sites may reflect the influence of activity occurring in subcortical limbic structures such as the hippocampus.

THE SUPRAMAMMILLARY NUCLEUS AND ASCENDING MODULATION OF HIPPOCAMPAL THETA FREQUENCY

In rodents, hippocampal theta rhythm can be observed over an almost two octave frequency range (4-12 Hz.), and although in humans, theta is defined as 4-7Hz, this still represents a considerable frequency range. A range of frequencies would be expected if, as suggested above, a function of theta is to invoke resonant activity in, and thus select, a variable repertoire of reentrant loops. Further, it would be expected that as the frequency of theta is critical to information processing in the structures in which it occurs, considerable precision and specificity might be expected in its control. However, until recently it was thought that the frequency of theta was determined by the intensity of relatively undifferentiated tonic activity ascending from the reticular formation, reflecting for instance an animal's state of "arousal" (O'Keefe and Nadel, 1978; Gray, 1982). In this section, we will outline evidence that in fact, oscillatory or phasic neural activity in the supramammillary (SuM) region is, at least in some behavioural states, responsible for determining theta frequency in the hippocampus (though see Kirk, 1998 for extensive discussion of this issue). The implication is that "theta" can occur independently from the septo-hippocampal system and that frequency coding of theta at the level of SuM reflects a considerable degree of information processing at the level of the diencephalon.

As noted above, there is a large body of research that indicates that the occurrence of hippocampal theta, and the frequency at which it occurs, is critically dependent on afferents from the medial septum/vertical limb of the diagonal band of Broca complex (MS/vDBB). Lesions of the MS/vDBB abolish theta. Petsche et al. (1962) recorded from medial septal cells that discharged in rhythmic bursts at the frequency of ongoing theta. The total output of these cells is in phase with theta and each has a stable phase relationship with ongoing hippocampal theta. Further, stimulation of the MS at theta frequencies ("septal driving") drives theta at the frequency of stimulation (Stumpf, 1965; James et al., 1977). Collectively, this evidence has led to the idea that the MS/vDBB acts as a pacemaker for hippocampal theta (see Stewart and Fox, 1990 and Kirk, 1998 for reviews).

What then determines the frequency of rhythmic bursts in the MS/vDBB? High frequency (100 Hz) stimulation in a number of midbrain sites has been found to be effective in eliciting theta (Vertes, 1982; 1986). Stimulation of the magnocellular reticular nucleus pontis oralis (RPO) has been shown to be particularly effective, and has been proposed to be the origin of the ascending "synchronizing" system involved in producing theta (Vertes, 1982, 1986). The frequency of septal cell bursting (Petsche et al., 1962, 1965) and that of hippocampal theta (Stumpf, 1965) elicited by high frequency reticular stimulation is proportional to the intensity of stimulation. Thus, the frequency of theta paced by the MS/vDBB is proportional to the tonic activation it was assumed to receive from inputs ascending directly from the reticular formation (Stumpf, 1965). Hence, it was argued that the MS/vDBB acts as an intensity/frequency transducer (Gray, 1982; O'Keefe and Nadel, 1978).

It was suggested that a likely mechanism underlying intensity/frequency transduction in the MS/vDBB was phasic recurrent inhibition (Klemm, 1976; Tombol and Petsche, 1969). However, it has been found that the application of GABA (A or B) agonists or antagonists in the septal area does not alter the bursting frequency of septal cells (Dutar et al., 1989; Lamour et al., 1984). In addition, septal administration of benzodiazepines (diazepam and CDP), that act at the benzodiazepine-GABA-chloride ionophore complex to enhance the effects of GABA, did not alter the frequency of reticularly-elicited theta in the urethane anaesthetized rat (Kirk and McNaughton, unpublished observations). This is in contrast to systemic administration of benzodiazepines in freely moving animals (McNaughton and Morris, 1987). Similarly, other neurotransmitters found in the MS/vDBB (5HT and ACh) do not appear to alter the frequency of septal cell bursting (Dutar et al., 1989). However, as noted, recent work suggests that the MS/vDBB receives information that is already frequency coded. That is, it receives phasic information in the ascending system, the frequency of which determines the frequency of septal bursting and that of hippocampal theta. The evidence outlined below suggests that the SuM is the site at which this could take place.

Initial impetus for investigations of the SuM came from studies by Vertes (1986; Vertes and Martin, 1988) who injected HRP into the medial septum and its principal ascending afferent fibre tract, the medial forebrain bundle (MFB). He found that, contrary to his expectations, retrograde labeling in the RPO was sparse. In contrast, there was substantial labeling in the SuM. Vertes argued that it is likely that RPO afferents synapsed in the SuM, and that SuM afferents are sent, via the MFB, to the MS/vDBB (Veazy et al., 1982; Vertes, 1992; Vertes and Martin, 1988). That is, the SuM acts as a relay in the ascending theta-synchronizing system. The suggestion that in addition the SuM is involved in the modulation of theta frequency was initially made by Kirk and McNaughton after the discovery of theta-rhythmic SuM cell activity that occurred independently of hippocampal theta (Kirk and McNaughton, 1991). Considerable support for this notion was provided by the results of our procaine mapping studies (Kirk and McNaughton, 1993). These studies will be briefly outlined here.

In procaine mapping studies in urethane anaesthetized (Kirk and McNaughton, 1993) and in unanaesthetized rats (McNaughton et al., 1996) we have shown that theta elicited by high frequency stimulation (100 Hz) in the

RPO of urethane anaesthetized rats is differentially effected by procaine infused at different points in the ascending theta-synchronizing pathways. For example, infusions of procaine (0.5 μl; 20%) caudal (or in afferents) to the SuM, but rostral to the RPO, reduced the frequency of reticularly-elicited theta. Infusions rostral to (or in efferents from) the SuM, up to and including the MS/vDBB reduced the amplitude of theta, but had no effect on frequency. Infusions into the SuM itself reduced both the frequency and amplitude of theta. On the basis of these results we proposed that the transduction of the intensity of reticular activation to the frequency of the resultant theta, takes place in the SuM region rather than in the MS/vDBB. The frequency coded (i.e. phasic) information is then fed, probably via the MFB, to the MS/vDBB.

That intensity/frequency transduction occurs in the SuM itself was given considerable support by our previous finding that multi-unit activity recorded from the SuM was rhythmic at the frequency of, and phase locked to, ongoing hippocampal theta (Kirk and McNaughton, 1991). Theta-rhythmic discharge in the SuM would certainly be expected if the SuM acts as an intensity/frequency transducer. Subsequent single-unit recording from the SuM confirmed the multi-unit results in spontaneous (Bland et al., 1995; Kocsis and Vertes, 1994) or reticularly-elicited theta states (Kirk et al., 1996). Further, rhythmic multi- (Kirk, 1997), and single-unit (Kirk et al., 1996) activity in the SuM survived septal procaine infusion that abolished hippocampal theta. Theta-rhythmic SuM discharge (elicited by RPO carbachol) also persisted after bilateral transections rostral to the SuM (Kirk et al., 1996). These data add further support for the idea that generation of theta can occur in the SuM independently of that in the septo-hippocampal system and that the predominant direction of rhythmic influence during theta ascends from the SuM to the septo-hippocampal system rather than vice versa (see Figure 1A). However, it should be noted, there is also evidence for descending influences to the SuM during theta and other hippocampal EEG states (Kirk and McNaughton, 1991; Kirk, 1997, 1998).

It should be noted that although ascending input from the SuM influences the frequency of hippocampal theta, it is probably not necessary for the occurrence of theta *per se*. Septal isolation reduces the rhythmical bursting of septal cells to approximately 3-4 Hz. (Brazhnik and Vinogradova, 1986; Vinogradova et al., 1980), but does not abolish it. It is probable therefore, that at least a proportion of septal bursting cells are intrinsically autorhythmic, but without ascending input, fire at a low rate and in insufficient numbers to induce rhythmical activity in the hippocampus. In a recent computer simulation, Denham and Borisyuk (2000) found that oscillation in septo-hippocampal circuitry is stable and at a constant frequency across a wide range of parameters in the absence of external frequency modulation. However, in the intact rat it is possible that an appropriate (non-phasic) input results in septal cell bursting being expressed as hippocampal theta, possibly via a process of intraseptal recruitment (Brazhnik and Vinogradova, 1986). Under reticular stimulation, ascending phasic input, coded in the SuM, may predominate and entrain septal bursting to a higher frequency. There is evidence from other systems (Ayers and Selverston, 1977) and computer models (Rinzel and Ermentrout, 1989) that auto-oscillators may be entrained in this way. As mentioned above, low frequency stimulation of the septum can drive hippocampal theta
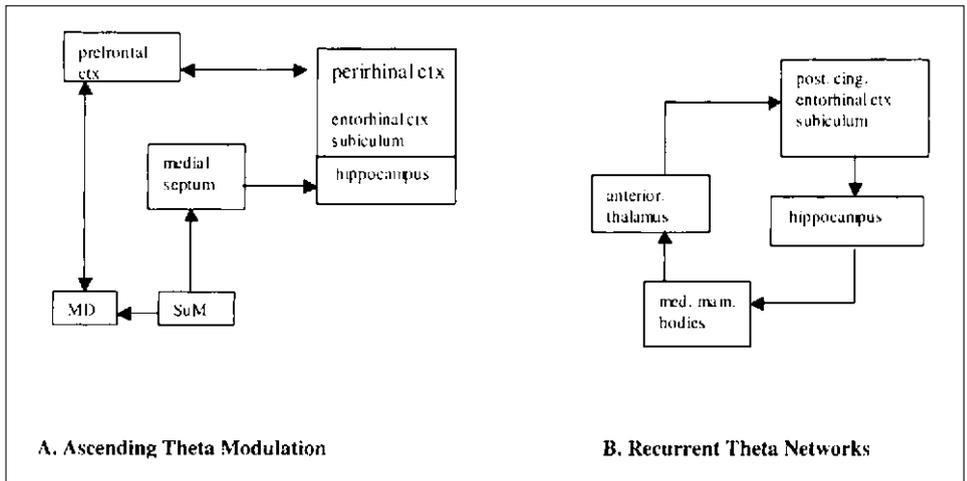
Fig. 1 – *Schematics of the pathways involved in A. ascending theta modulation and B. recurrent theta networks described in text. Abreviations: ctx – cortex, MD – mediodorsal thalamus, SuM – supramammillary nucleus, post. cing. – posterior cingulate, med. mam. bodies – medial mamillary bodies.*

(James et al., 1977; Stumpf, 1965). It can also entrain septal bursting cells to the stimulation frequency (Brazhnik et al., 1985; Brazhnik and Vinogradova, 1986). This has been taken as evidence for the septal pacemaker hypothesis (though see Stewart and Fox, 1990). However, these data, and the fact that low frequency stimulation of the MFB also entrains septal bursting cells (Brazhnik and Vinogradova, 1988), are also consistent with the present hypothesis that the MS/vDBB receives frequency-coded information during hippocampal theta.

On a similar note, whereas procaine infused into the SuM has been shown to attenuate the amplitude and frequency of reticularly-elicited hippocampal theta in urethane anesthetized (Kirk and McNaughton, 1993; Thinshmidt et al., 1995) and freely moving rats (McNaughton et al., 1996), lesions of the SuM did not obviously affect spontaneously-occurring theta in the unanaesthetized animal (Thinshmidt et al., 1995). It should be noted that in this particular study (Thinshmidt et al., 1995), the theta in question was low frequecy and of a limited range. Nevertheless, it seems likely, that as suggested above, rhythmical activity in the SuM is required for modulation of theta frequency but is not necessary for the expression of theta *per se*. Further, it has been demonstrated that lesions of the RPO produced little obvious change in hippocampal theta in freely moving animals (Farris and Sainsbury, 1990). Hence, it is possible that the SuM is only involved in the modulation of theta frequency when in receipt of high levels of activation from the RPO that may normally only occur in particular behavioural states (Vertes, 1982; 1986) or during RPO stimulation. Input from the posterior hypothalamus (see below) may be particularly important for the expression of theta generally. However, a variety of other pathways may also be involved. For example, cells of the pedunculopontine tegmentum (PPT) also project directly to the MS/vDBB (Woolf and Butcher, 1986), and stimulation of (Vertes, 1982), or infusion of carbachol into (Vertes et al., 1993)

the PPT has been shown to effectively elicit theta. There is recent evidence that a number of divergent projections from the PPT (in addition to that to the MS/vDBB) may cooperate in the gating of theta (Swain and McNaughton, 1996). It should also be noted that although SuM procaine (or CDP) infusion reduces the frequency of reticularly-elicited theta in freely moving rats, the reduction is much less pronounced than in urethane anaesthetized rats. It is likely therefore that, in the freely moving animal, frequency-modulating mechanisms other than those in the SuM are active. Vertes (1982, 1986) describes three ascending synchronizing systems that appear to take distinct paths through the caudal diencephalon. Additional transducers (other than the SuM) or relays (other than the PH, see below) are therefore a distinct possibility (see discussion in McNaughton et al., 1996).

Theta Activity in Mammillary Nuclei, Anterior Thalamic Complex, and Reentrant Limbic Circuitry

As with those in the SuM, neurons in the mammillary nuclei have also been shown to discharge rhythmically at theta frequencies (Bland et al., 1995; Kirk et al., 1996; Kocsis and Vertes, 1994; Mignard et al, 1987), and repetitive bursts have been recorded *in vitro* from the medial (MM), or lateral (LM) mammillary nucleus (Alonso and Llinas, 1992; Llinas and Alonso, 1992). As with hippocampal theta, this activity in the mammillary nuclei may subserve their proposed role in memory in general (Mair et al., 1979), and in spatial memory in particular (Sziklas and Petrides, 1993; Sziklas et al., 1996).

In contrast to theta-related SuM cells, the discharge properties of MM theta-phasic cells are considerably affected by septal procaine infusion (Kirk et al., 1996). The discharge of MM phasic cells became non-rhythmic during RPO stimulation after septal procaine. Also, their discharge rates were severely attenuated immediately subsequent to septal procaine infusion. Thus, it appears that MM cell discharge *per se*, and rhythmic discharge in particular is dependent on input descending from the septo-hippocampal system. Results of partial coherence analysis also suggested that rhythmical, theta-related MM discharge (but not that of SuM) is driven by descending inputs originating in the hippocampal formation (Kocsis and Vertes, 1994). The MM is likely to receive descending input originating in the hippocampus and relayed via the subiculum or lateral septum (Allen and Hopkins, 1989; Swanson and Cowan, 1977;1979).

Based on the known projections of the MB it has been proposed that the MM relays theta-frequency information to the anterior thalamic nuclei (AT; Llinas and Alonso, 1992; Alonso and Llinas, 1992). The AT may then relay theta activity back to the hippocampus (via connections to the subicular, retrosplenial posterior cingulate) and entorhinal areas (van Groen and Wyss, 1995). Hence, theta-frequency neuronal activity maybe transmitted around a circuit originally described by Papez (1937).

If theta is present throughout the nuclei of Papez loop, then theta-rhythmic neuronal activity would be expected in the AT (particularly in those nuclei in receipt of projections from the MM (i.e. anteroventral (AV), anteromedial (AM)

and anterodorsal (AD) nuclei) during hippocampal theta EEG. To test this we recorded hippocampal field EEG (in theta and non-theta (Large-amplitude irregular activity (LIA) hippocampal EEG activity) from the stratum moleculare of the hippocampus of urethane anaesthetized rats while recording unit activity in nuclei of the AT (Kirk et al., 1998; Kirk, submitted). Clear theta-rhythmic unit activity, coherent (0.4-0.7) with the hippocampal theta field EEG was found in the AV, AM and AD nuclei of the anterior thalamic complex. Overall, these findings are consistent with the proposal that theta-frequency activity is relayed from the septo-hippocampal system, via the MM to anterior thalamic nuclei. The AV and AM and AD may then transmit theta-modulated activity back to parahippocampal structures, and hence back to the hippocampus itself (see Figure 1B).

Based on an extensive review of the literature, Aggleton and Brown (1999) have recently proposed that the hippocampal-anterior thalamic axis as described above is the neural substrate responsible for the encoding and subsequent recall of episodic memory or (in animals) allocentric spatial memory. The fact that coherent theta activity is found in all nodes of this recurrent circuit lends support to this contention, at least to the extent that temporally coordinated neural activity in the system suggests that integrated information processing may be taking place. Consistant with at least the spatial component of this proposal, "head direction" cells have been recorded in the AD (Blair et al., 1997; Taube, 1995) and subiculum (Goodridge and Taube, 1997), while "place cells" are recorded in the hippocampus (see Muller et al., 1996; O'Keefe and Recce, 1993 for reviews). Sensory systems converging on the anterior thalamus may be responsible for the modulation of "head direction" cells that have been found there. AT projections to the subicular complex may tune head direction cells there and this directional information is presumably integrated into the place code in the hippocampus. Consistant with these proposals, spatial working memory is shown to be impaired after lesions of the MB (Sziklas and Petrides, 1993), anterior thalamus (Aggleton and Brown, 1999; Byatt and Dalrymple-Alford, 1996), or subicular complex (Taube et al., 1992). Further, Vann et al. (2000) have shown increases in activation (as indexed by Fos protein expression) in the subicular complex and in AD, AV and AM.

It should be noted here that Parmeggiani et al. (1974) and Gray (1982) have also previously suggested a role for theta in the anterior thalamus in the control of hippocampal output and timing of information flow around Papez circuit. It has recently been suggested that (Lisman and Idiart, 1995) that activity patterns associated with multiple "memories" may be stored in a neural network in gamma (e.g. 40Hz) oscillations "nested" in theta-frequency oscillations similar to those recorded in the hippocampus. In this model, each memory is stored as distributed discharge in a different high frequency (40Hz) subcycle of the low frequency hippocampal oscillation. Memory patterns repeat on each low frequency cycle allowing serial processing and tuning on the memory by reentrant processes (see also Edelman, 1993). Papez circuit may represent one such reentrant loop, possibly involved with integrating or comparing ascending afferent information at the level of the MB and at the level of AT with a descending representation of information currently stored in the hippocampal-parahippocampal network.

An involvement of these systems is suggested for non-spatial mnemonic processes also. It has been proposed for instance, that output from various functional domains of the hippocampus map onto hypothalamic systems (including MB) mediating different classes of goal oriented behaviour (Risold and Swanson, 1996) which then map back onto particular regions of the hippocampal complex. Interactions between the activity of hippocampal, cingulate, subicular and anterior thalamic neurons have been demonstrated during avoidance conditioning in rabbits (Kubota et al., 1996) suggesting (to them) a stable mnemonic representation of the associative significance of the CS which is used as a comparator to inhibit behaviour in response to unexpected events. Finally, lesions in the MB and AT and apparently correlated mnemonic deficits are observed in Korsakoff's patients (Mair et al., 1979).

SuM, Medial Dorsal Thalamus and Prefrontal Cortex

In addition to theta-rhythmic cells in the nuclei of the AT, we also found multi-unit activity coherent with hippocampal theta EEG in the medial dorsal nucleus of the thalamus (MD; Kirk et al., 1998; Kirk, submitted). The MD does not receive input from the mamillary bodies so is unlikely to be part of the same reentrant circuit as AV, AD and AM. However the MD is in receipt of afferent from the SuM (Vertes, 1992), so in that respect it is not surprising that theta-related neural activity is found there. In contrast to the role of AT nuclei in episodic memory and allocentric spatial memory discussed above, Aggleton and Brown (1999) propose that the MD is part of a network involved in item recognition and familiarity judgements. Other key structures in this system are the prefrontal cortex and, in particular, the perirhinal cortex. Aggleton and Brown cite an extensive literature in defence of this position that will not be repeated here. Nevertheless, there is some debate as to how dissociable the MD-perirhinal and hippocampal-AT systems are in functional terms (e.g. Bilkey, 1999; Foster, 1999; Markowitsch, 1999) and the extent to which prefrontal cortex is part of the former (e.g. Parker, 1999). Of particular interest here is that the MD-perirhinal and hippocampo-AT systems may well be capable of independent theta generation and, on the current argument, independently co-ordinate task-related activity between nodes in their own network (see Figure 1A). It is probable though, that both item recognition and episodic processes are required in many behavioural tasks (spatial navigation for instance). Appropriate coherent theta activity across particular nodes would facilitate transfer of information between systems.

It should be noted however that independent generation of theta in the two systems has yet to be demonstrated. In the subsequent section we will describe pilot experiments that suggest that differing mnemonic tasks give rise to different scalp topographies of theta power in humans. It is possible that appropriate tasks manipulating familiarity versus episodic processes may yield different scalp topographies of theta power reflecting differential activation of the perirhinal-MD and hippocampo-AT systems. Although a very much oversimplified position (see below), based on the theta pathways illustrated in Figure 1, we might propose that frontal theta may be seen at greater power in tasks requiring familiarity judgements, for instance, and temporal theta in tasks requiring recall.

SCALP RECORDING OF CORTICAL THETA IN HUMANS

There has been uncertainty regarding the existence of memory-task dependent theta activity in humans. Theta has been regularly recorded from the frontal midline scalp electrodes, but in such a variety of tasks its significance is unclear (see Inanaga, 1998 for review). Certainly its relationship to hippocampal theta has been particularly uncertain. Klimesch and others have shown increases in power in theta-band in human scalp recorded EEG that occur selectively during the encoding of new information (Klemisch et al., 1994; Burgess and Gruzelier, 1997; see Klemisch, 1999 for review). However, with respect to spatial memory, in experimental rats, hippocampal theta is reliably elicited during exploratory and spatial memory behaviours. The first evidence that the human hippocampus was activated during similar tasks was provided in a PET study that showed intense activation of the right hippocampus while subjects performed in a previously learnt virtual 3D maze (Maguire et al., 1996). Using a similar virtual maze task theta activation has recently been recorded from intercranial electrodes in frontal and temporal regions in pre-operative epileptic patients (Kahana et al., 1998).

In pilot human EEG work in our laboratory we have used 128 channel recordings of EEG to record theta non-invasively in a spatial memory task (navigation in a virtual 3D maze) and in a test of verbal working memory (Mackay et al., 2001). If the topography of scalp recorded theta is to be at all useful to partial out the contributions of different networks in different memory tasks then we would certainly expect clear differences between tasks as disparate as the Sternberg working memory task and the performance in a spatial maze. The results of a FFT power (amplitude) map, spline-fitted to a spherical skull model are shown in Figure 2.

Theta activity, at least as defined by a clear peak in the theta range after spectral analysis, was quite widely distributed across the scalp. However, we found different distributions of maximal power theta across the frontal and left and right temporal regions of the scalp in these two tasks that suggests differentially activated neural substrates in different tasks. Here it can be seen in that different types of memory task have markedly different peak power (dark) distributions. Theta during the retention period in the Sternberg task is distributed frontally and left temporally, while that during the performance of the 3D maze is distributed frontally and right temporally. This pattern of results is in general agreement with the previous results of Kahana et al. (1998) who showed that task-related theta occurred in a greater number of sites in the right temporal lobe in a spatial maze task, of Raghavachari et al. (2001) who found a greater number of sites in the left temporal lobe in a working memory task, and that of Sarthein et al. (1998) who also found high coherence in the theta range across more right hemisphere electrodes in the retention phase of a working memory task. This probably indicates access to left hemisphere dominant linguistic processes (storage of alphanumeric characters) in the working memory task, and right hemisphere dominance in the spatial task (De Renzi, 1978; Corballis, 1991).

In this, and the Kahana et al. (1998) experiment it is unlikely that theta activity is volume conducted from the hippocampus to the surface. It is much
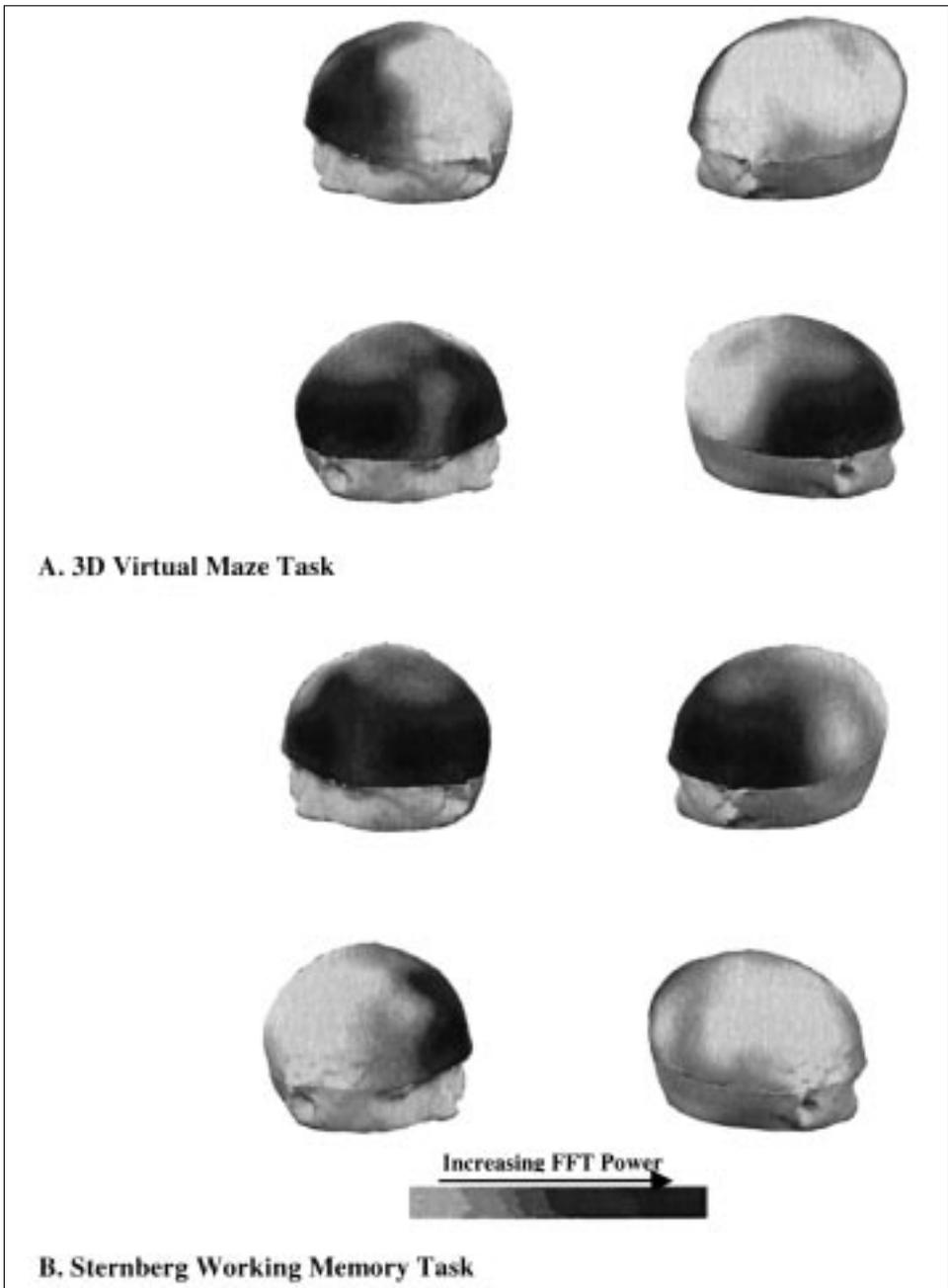
Fig. 2 – *Spherical spline interpolation (Matlab software available at http://www.cnl.salk.edu: see e.g. Makeig et al., 1999) average FFT power from 128 channel EEG for the two tasks. In each panel four perspectives of the same plot are shown. A. Theta power distribution during performance of the 3D virtual maze. Maximal power can be observed predominantly over the right temporal region and frontal regions. B. Theta power distribution during the retention interval of a Sternberg working memory task. Maximal power can be observed predominantly over the left temporal region, and also in the frontal regions.*

more likely to be transmitted to surface cortical areas via the pathways described above and shown in Figure 1. It is generally assumed that cortico-hippocampal interactions will take place via parahippocampal structures such as the entorhinal cortex, and certainly this is the pathway proposed by Miller (1991) for theta-modulated cortico-hippocampal resonant loops. It is of note however that we (Dickson et al., 1995) observed the majority of entorhinal theta-modulated cells in layers II or III in anaesthetised rats. These layers are responsible for the input from neocortex to hippocampus (Steward and Scoville, 1976; Amaral and Witter, 1995). Very few theta-modulated cells were observed in entorhinal layers V and VI that are responsible for hippocampal output via the entorhinal cortex. Similarly, in freely-behaving rats, Chrobak and Buzsaki (1994) did not observe significant theta-modulation in output layer cells of the entorhinal cortex. On the current evidence therefore, we assume that theta in entorhinal cortex modulates cortical input to the hippocampal system, but that theta-modulated is via another route. The most likely candidate is via lateral septum and via the medial forebrain bundle to diencephalons (McLennan and Miller, 1974; 1976; Leranth et al., 1992; Witter et al., 1992).

Although we have demonstrated differential topographies of theta power in different memory tasks, these experiments were not designed to specifically address the model of Aggleton and Brown (1999), and nor do they. It is probable in fact, that in both the working memory and the spatial tasks we employed that both the MD-perirhinal and hippocampo-AT systems are activated. Further, with respect to frontal and temporal projections there is considerable overlap (at least broadly) between the two systems. Both systems (on the Aggleton and Brown view; see also Kievit and Kuypers, 1977; van Groen et al., 1995; 1999; Barbas, 2000; Ongur and Price, 2000) have projections to prefrontal and temporal cortex and as such may not be grossly separable in terms of the magnitude of cortical theta activation in temporal versus frontal regions. However, Aggleton and Brown cite evidence that prefrontal activation may not be necessary for some types of familiarity judgement, but necessary for others. Recent PET studies indicate that temporal activation is highest for novel stimuli, whereas prefrontal activation is highest for novel rearrangements of familiar stimuli (Dolan and Fletcher, 1997). Whether these observations will correlate with differential increases in theta power in temporal and prefrontal cortex remains to be seen.

Finally, and more generally, it seems likely that given differential projection topographies of AT nuclei and MD to regions within prefrontal and temporal cortex finer distinctions may be made on the basis of theta-band topographies across different mnemonic tasks. To achieve this however, more refined techniques will be necessary. Firstly, adequate spatial sampling of the EEG will be required, hence dense-array EEG will need to be recorded (see e.g. Tucker, 1993). In addition, it will probably be necessary to account for the spatial blurring effects of the skull and scalp on the electrical signal arising from even quite shallow cortical sources. Algorithms that incorporate MRI derived realistic head models and "deblur" the spatial noise due to transmission through the scalp have been developed (Gevens, 1999) and increased use of these techniques may yield spatial resolution fine enough to distinguish between different topographies of EEG activation in different mnemonic tasks within frontal and temporal areas for example.

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