Frontal-midline theta from the perspective of hippocampal "theta"

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ARTICLE INFO

ABSTRACT

Electrical recordings from the surface of the skull have a wide range of rhythmic components. A major task of analysis of this EEG is to determine their source and functional significance. The hippocampal "theta rhythm" has been extensively studied in rats and its rhythmicity has recently been shown to be functionally significant, *per se*. Here, we use relevant aspects of the hippocampal literature to provide perspective on one of the most studied human EEG rhythms: frontal-midline theta. We review its electrographic features, localization, prevalence, age distribution, behavioural modulation (particularly in relation to working memory, spatial navigation, episodic memory, internalised attention and meditation), relationship to personality, drug interactions, neurochemical relationships, and coherence with rhythmic activity at other sites. We conclude that FM-theta, like hippocampal theta, appears to play a role in (or at least occur during) processing of memory and emotion. It is correlated with working memory and/or sustained attention; but this does not entail a role in function since clear behavioural correlates of hippocampal theta have been demonstrated that are not sensitive to hippocampal damage. FM-theta is increased by anxiolytic drug action and personality-related reductions in anxiety, whereas hippocampal theta is decreased by anxiolytic drugs. In animals, frontal theta and hippocampal theta can be phase-locked or independent, depending on behavioural state. So, the cognitive functions of FM-theta, and their relationship to hippocampal theta, are unclear and definitive evidence for functional involvement in cognitive or emotional processing is lacking. One possible solution to this problem is analysis of FM-theta in animals—provided homology can be determined. The issues of sporadicity and low incidence of FM-theta also need to be addressed in the future. Changes in functional connectivity, indicated by changes in coherence, are also a largely untapped resource. We suggest that the most hopeful path to assessing the functions of FM-theta will be through the use of drugs, and the variation of their effects depending on baseline levels of FM-theta. Finally, we review some theories of theta function. Despite the apparent richness of the current data, we conclude that it is difficult (and may ultimately be impossible) to formulate a theory that attributes a specific cognitive function to FM-theta. However, the theories share some general computational assumptions and these should be a useful guide to future work and, ultimately, a definite theory of the function or functions of FM-theta.

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1. Introduction

1.1. A focus on "theta rhythms"

Electroencephalographic (EEG) recordings from the surface of the scalp are replete with rhythmic components. In humans, the EEG rhythms are usually divided into different frequency bands including delta (∼0–4 HZ), theta (∼4–8 Hz), alpha (∼8–12 Hz), beta (∼13–30 Hz) and gamma (∼40 Hz). However, there are often discrepancies between studies regarding the specific parameters of these bands. The choice of a specific frequency band and subdivisions within a band are intended to map bands to distinct brain functions, and so to map them to physiological and psychological processes that are specifically associated with that band or sub-band. A major task of EEG analysis is to determine the source and functional significance, if any, of the observed rhythms.

This review focuses on the rhythm described as frontal-midline theta (FM-theta) in the human EEG. The definition of FM-theta is considered below. Although theta recorded from other scalp locations such as above the medial temporal lobe (Guderian and Duzel, 2005) is starting to be studied in more detail, the bulk of research to date has focused on FM-theta. Likewise, although task-related alpha rhythm has been studied, task-related changes in theta have been studied more extensively. For the purposes of the initial inclusion of data in this review, FM-theta was taken to potentially include all rhythmic oscillations that

- are maximal in the frontal-midline region: F3, Fz, F4;
- have a frequency in the range 4–8 Hz or, potentially, somewhat higher;
- and can be observed either in the raw EEG or through event related averaging or analysis of power spectra.

Although the main focus is on FM-theta, so defined, details regarding the properties of other theta rhythms particularly hippocampal "theta" in the rodent will be outlined, where necessary. In the body of the review our purpose in making such comparisons has been to provide a context for interpretation of particular results obtained with FM-theta—and we have not assumed any specific functional relationship between FM-theta and the rhythms with which we have compared it. However, two major questions addressed in the discussion are whether FM-theta is of functional significance and whether it is connected to the "theta rhythm" generated by the hippocampus (Arnolds et al., 1980b; Bland, 1986; Cantero et al., 2003; Ekstrom et al., 2005; Green and Arduini, 1954; Halgren et al., 1978; Meador et al., 1991; Raghavachari et al., 2006; Rizzuto et al., 2003; Sainsbury, 1998; Sano et al., 1970; Vanderwolf, 1969). Critically, if different behaviours or functional states are associated with the theta rhythm recorded in humans versus that recorded in rats then different functional mechanisms are implicated in their generation (O'Keefe and Burgess, 1999). Conversely, in as much as human superficial theta at any site is homologous to rat hippocampal theta, there is the possibility of a transfer of the large amount of knowledge accumulated regarding rat hippocampal, and theta, functions to human theta. To assess this, comparative research needs to be carefully conducted using paradigms in humans that closely resemble those used with rats. A major purpose of this review is to generate specific testable hypotheses for future investigations.

1.2. From rhythm to function

Rhythmic oscillation is likely to occur in excitatory neural circuits that are recursively connected whenever these are not highly damped. Epileptic seizures are an extreme form of such non-damped activity. Such intrinsic oscillations, like the humming of a string in the wind, are a consequence of a simple flow of energy through an elastic system and, since they result from huge numbers of neurons firing synchronously, reflect a lack of detailed coding of information. As such these rhythms are likely either to lack function or to be signs of dysfunction.

Functionally significant rhythms can occur when a specific external pacemaker forces significant numbers of neurons (whether recursively connected or not) to fire and become silent at approximately the same time as each other. The pacemaker determines when neurons may fire but, provided only a modest proportion of neurons are active at any one time, large amounts of information can be encoded by which neurons in fact fire at the appointed time. The hippocampal "theta" rhythm (which is in the region of 4–6 Hz in animals such as rabbits, cats and dogs but occurs in the range 5–14 Hz in freely moving rats) is controlled by a pacemaker in the medial septum (Brucke et al., 1959; Gogolák et al., 1967, 1968; Stumpf et al., 1962). This sends an inhibitory phasic signal to the hippocampus (Leung, 1998) and neurons receiving excitatory input fire predominantly when the inhibition is released (Smythe et al., 1992). Information may be encoded not only by which cells fire but also by the precise phase relation of their firing to the ongoing rhythm (O'Keefe and Recce, 1993). Similarly, cortical alpha is considered to be generated, on occasion, by input from other cortical and thalamic networks (Klimesch, 1999). It is likely that control of phasic firing by pacemakers is important for the control of processing by the loops that pass information recursively from neocortex to the hippocampus (Miller, 1989, 1991) or around related circuits (Buzsáki, 2006; Parmeggiani et al., 1971).

It is possible that, at times, other external pacemakers than the septum control hippocampal theta; and that the hippocampus could show theta as a form of auto-oscillation. However, at present,

we believe there is no evidence that this occurs under normal physiological circumstances in freely moving animals.

Until recently, it was not known whether the synchronous rhythmic activity giving rise to any EEG rhythm had direct functional significance or was just a correlated epiphenomenon of functional activity. However, it has recently been shown, using a "brain by-pass" technique that restoring hippocampal rhythmicity, without any restoration of the normal spatial and temporal patterns of individual cell firing, can restore psychological function that is lost when rhythmicity is blocked (McNaughton et al., 2006). This finding with hippocampal theta suggests that other rhythms may have similar functional significance. However, as we shall see, what is known about the occurrence and functional significance of hippocampal theta implies that there are major problems in using correlational approaches to determine the underlying functions of any brain rhythmicity.

1.3. A hippocampal perspective

In this review, we assess the extent to which FM-theta has related properties to those of hippocampal "theta" and theta recorded from other cortical brain regions. The main reason for taking a hippocampal perspective is that, at the general level, the huge literature on hippocampal theta provides a strong framework for asking detailed questions about FM-theta without any need to assume identity or homology between the two. That is, known relations or lack thereof between hippocampal theta, behaviour and function can provide a basis for judging the value of equivalent evidence in relation to FM-theta. However, at the specific level, we also need to determine to what extent hippocampal theta and FM-theta might be directly related. We will argue that each may occur independently while also, on occasion, becoming locked together in coherent oscillations.

We will start by defining FM-theta, and listing similar phenomena that are clearly not FM-theta, and then consider phenomena that are indeterminate. We will then concentrate on clear FM-theta and outline its features; electrographic characteristics; possible sources; prevalence; behavioural associations; neurobiological associations; and drug interactions. We will also, where possible, compare these at a general level with what is known of hippocampal theta—which can often illustrate potential pitfalls in interpretation of the human EEG data.

1.4. Pragmatism versus theory

In the bulk of this review we have taken a largely pragmatic approach that avoids a strongly theoretical focus. There are three reasons for this. First, we believe that a balanced and, as far as possible, comprehensive presentation of the data as they now stand will more readily lead to a proper theory of the function or functions of theta if it is not filtered by current theoretical preconceptions. Second, as we discuss in Section 8.1, current theories appear to have in common the view that theta acts generally to control processing in neural circuits and so its apparent cognitive function at any point in time will depend on which circuits it is controlling rather than being inherent to its rhythmicity. Thirdly, the bulk of the data are necessarily correlational—and here the hippocampus provides us with a useful yardstick. "Despite seven decades of hard work on rabbits, rats, mice, gerbils, guinea pigs, sheep, cats, dogs, Old World monkeys, chimpanzees and humans by outstanding colleagues, to date, there is still no agreed term that would unequivocally describe behavioural correlate(s) of hippocampal theta rhythms" (Buzsáki, 2006, p. 21). For all these reasons we will leave theoretical considerations to the final section.

2. Electrographic features

2.1. What is theta?

The theta frequency in the human EEG was initially defined as 4–7 Hz (Walter and Dovey, 1944) simply to provide an intermediate frequency band between delta and alpha. The name 'theta' was given with reference to the 'thalamus' where the rhythm was thought to arise. Later, theta frequency was defined as 4–8 Hz (IFSECN, 1974). If such bands are defined by independent neural processes, it is clearly open to question whether they are exclusive. Can "theta", functionally defined, extend into the alpha range, for example?

FM-theta in normal, awake, adults has been the focus of research because its amplitude and duration are exceptional. At other sites there is, by and large, only a small amount of power at theta frequencies and no clear bursts in individual traces (Niedermeyer, 1999). Important distinctions can also be made between tonic and phasic types of theta (Klimesch, 1999). It is suggested that phasic and tonic types of theta have different functions and generators. Both phasic and tonic forms of theta have been correlated with a number of different behaviours. In particular phasic theta occurs in response to some event or activity and has a discrete temporal and topographical appearance over frontal regions. In contrast tonic theta tends to coincide with more global and stable characteristics or phenomena and to have a more diffuse topography. Hippocampal theta was so called because its initial discovery was in animals in which hippocampal rhythmicity was in the conventional human EEG theta range. "Hippocampal theta" is now defined less by its frequency than by the fact that its sources and sinks result from input from the medial septum (and produce rhythmic firing of hippocampal neurones) in all species. This homology has resulted in such hippocampal rhythmicity being termed "theta" in all species independent of the precise frequency band observed. As we noted above, the frequency of "hippocampal theta" can be as high as 14 Hz in the rat. Hippocampal theta rhythm in the rat is consistently generated prior to certain movements (Morris and Hagan, 1983; Vanderwolf, 1969) but also occurs in the complete absence of movement under conditions of high arousal (Sainsbury, 1998). In both cases it can be viewed as a sign of preparation for movement but in the latter case it is a preparation that does not in fact result in action.

The hippocampus has been postulated to contribute to cognitive functions such as spatial mapping (O'Keefe and Nadel, 1978) and relational memory (Cohen and Eichenbaum, 1993) and to emotional functions (Papez, 1937), particularly behavioural inhibition (Gray, 1982; Gray and McNaughton, 2000). All components of the hippocampal formation, including the entorhinal and posterior cingulate cortex as well as hippocampus proper (Gray and McNaughton, 2000; Leung and Borst, 1987), show theta activity.

Activity in the medial prefrontal cortex can be modulated by the hippocampus depending on the behavioural state of the animal (Jones and Wilson, 2005). This raises the issues of how far hippocampal theta may contribute to frontal theta and, given the known extensive variation in the frequency of the former, what is the frequency band of the latter.

2.2. What is FM-theta?

2.2.1. FM-theta in the EEG

The term FM-theta was coined by Ishihara and Yoshi (1972). They defined it as a distinct frontal-midline theta rhythm at 6–7 c/s and 30–60 μV lasting seconds during mental tasks such as continuous arithmetic addition. Table 2 presents information from studies that either provided FM-theta signal properties, or descriptive illustrations (an example of FM-theta is given in Fig. 1). These papers suggest that FM-theta is almost always around 6 Hz, though it can range from 5 to 7.5 Hz (between individuals). The amplitude is around 50–75 μV (and often higher than the average background amplitude). The waveform is basically sinusoidal, superimposed on the prevailing background. Within individuals, the frequency appears consistent within bursts and also between bursts within illustrated cases. Between individuals there are differences, and some do not demonstrate FM-theta at all. Typically, FM-theta appears in discrete bursts that last a few seconds but can range from 1 to >10 s. It tends to wax and wane (Mizuki et al., 1980) and there does not appear to be any time-locked relationship between the initiation of the task and the appearance of FM-theta (Gevins et al., 1997). For example, the amount of FM-theta ranged from about 20 to 110 s during a continuous Uchida-Kraepelin task lasting 5 m (Mizuki et al., 1980). (The Uchida-Kraepelin task involves continuous arithmetic addition of successive pairs of numbers where the second number of the previous pair is the first of the current pair.) FM-theta, therefore, can be described as a phasic, task-related modulation of the background EEG. However, some studies have clearly shown phase- and time-locked components during behavioural tasks. Where there is sufficient electrode cover to estimate the field, it is always fronto-central, with a maximum at, or just anterior to Fz.

2.2.2. FM-theta in the magnetoencephalogram: 'Frontal-mental-theta'

Magnetoencephalographic (MEG) recordings can also identify frontal-midline theta rhythms and provide complimentary data to EEG studies. MEG provides an insight into the tangential currents generated during encephalographic activity and is less contaminated by volume conducted currents through the layered structures above the cortex. As such, it is better suited to source analysis.

Sasaki et al. (1994b) coined the term 'frontal mental theta' to account for the MEG phenomenon of theta waveforms during
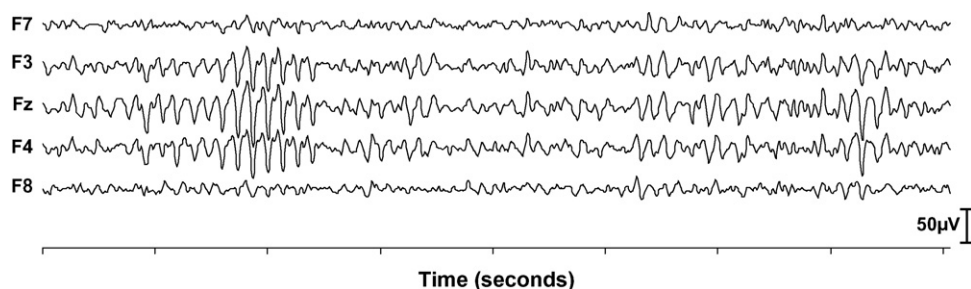

Fig. 1. Illustration of frontal-midline theta recorded during the performance of a continuous N-back working memory task. Two seconds into the EEG trace 6.5–7 Hz theta can clearly be observed at F3, Fz, and F4 with an amplitude of 50–75 μV. The theta activity has a peak at Fz and tends to wax and wane over time.

calculation and musical imagining and have subsequently studied MEG components of FM-theta (Sasaki et al., 1996b,c). These studies demonstrated that FM-theta and frontal-mental theta have identical frequencies, and similar waveforms (Sasaki et al., 1996c), although slightly differing distributions. Frontal-mental theta appears more broadly distributed in the frontal lobes when compared to FM-theta. But this is likely to reflect the differences in the features recorded by the two techniques—in studies where FM-theta has been synchronously recorded using scalp EEG and MEG it is reasonable to assume that frontal-midline theta and frontal-mental theta represent different projections of the same phenomenon. Iramina et al. (1996), Ishii et al. (1999) and Asada et al. (1999) have also employed synchronous EEG and MEG to study FM-theta (see under localization of FM-theta for details).

For the purposes of the remainder of the review, we will provisionally assume that frontal-mental theta recorded by MEG and FM-theta in the EEG represent the same underlying neural phenomena. However, further detailed research is clearly required to determine whether this is the case or not.

2.2.3. Signal processing and analysis of FM-theta and the ERP problem

A number of techniques are available for analysing the EEG signal including averaging and event related potential (ERP) analysis, event related desynchronization/synchronization ERD/ERS (Pfurtscheller and Lopes da Silva, 1999), fast Fourier transformation (FFT) (Thakor and Tong, 2004), and wavelet analysis (Basar et al., 2001a). These techniques capture information pertaining to time, power, and the frequency domain. Signal processing techniques such as FFT, ERD/ERS analysis, and wavelet analysis are a useful method of data compression and can reveal features of FM-theta under appropriate conditions. FFT analysis reveals the prominent frequencies within an EEG segment however it does not provide a detailed account of the temporal components of the EEG. In contrast, ERD/ERS (Pfurtscheller, 1992; Pfurtscheller and Aranibar, 1977, 1978; Pfurtscheller and Lopes da Silva, 1999) and wavelet analysis can help to determine changes in spectral power with a better temporal resolution. As such they provide powerful tools for investigating events that modulate rhythms such as FM-theta (e.g. behaviours and drugs). If a subject performs a task known to elicit FM-theta, and this is confirmed by visual analysis, then appropriate signal processing of data will reveal a peak around 5–7 Hz in frontal-midline electrodes (Harmony et al., 1999; Pellouchoud et al., 1999).

However, it should be noted that the reverse need not be the case. The Fourier transform, on which both simple power spectra and wavelet analyses are based, will convert any data series into a set of sine wave components. The presence of power at a particular frequency in a transform, then, does not provide any evidence that the underlying signal is rhythmic in the sense of repeating over multiple cycles. Power in the theta range could, for example, be generated by evoked potentials. Strictly, then, to interpret averaged power changes as evidence for changes in theta rhythm either sinusoidal rhythmicity should be demonstrated in individual raw traces or via autocorrelation of raw traces. This kind of check has often not been undertaken in the studies reviewed here.

There are a number of studies and theories that emphasise the importance of the phase of EEG oscillations in working memory (Givens, 1996; Jensen and Lisman, 1998), retrieval, and encoding processes (Hasselmo et al., 2002; Rizzuto et al., 2006). In contrast to signal processing techniques, averaging of the raw EEG is an effective method to tease out low amplitude event related potentials (ERPs) that are time- and phase-locked to an event while eliminating other signals. A critical question arising from this line of research is to what extent the averaged ERP is composed of discrete evoked potentials of a similar conformation and to what extent it results from phase reset

of ongoing rhythmicity—and to what extent it contributes to power in signal processing (Bastiaansen and Hagoort, 2003). Analysis of the ERP does reveal that components of this waveform are within the theta frequency range (Brankack et al., 1996; Bruneau et al., 1993; Yordanova and Kolev, 1996). Therefore, averaged ERPs at frontal-midline sites may be a form of FM-theta, or functionally homologous to it (Bruneau et al., 1993; Burgess and Gruzelier, 1997). Furthermore, an inverse relationship between frontal ERPs and pre-stimulus theta components has been demonstrated (Basar et al., 2001b; Yordanova and Kolev, 1997a, 1998). With the possibility of a consistent phase-reset, it is difficult to disentangle whether ERPs such as the N200-P300 complex are the result of phase-resetting of the ongoing EEG or the evocation of transient EEG events, or a combination of the two. To some extent this issue can be settled with simple averaged waveforms. Reset of ongoing theta in the hippocampus, for example, produces a clear damped oscillation with multiple peaks and troughs and a generally consistent peak–trough and trough–peak interval (Givens, 1996). Conversely, on a single sweep basis, an electrically evoked potential produces only one or two negative and positive components (Brankack et al., 1996) and, when averaged, these result in waveforms that are unlike damped oscillation in terms of both the limited number of peaks and troughs and the marked variation in peak–trough and trough–peak intervals.

However, averaging the human scalp EEG may not be an effective method to detect phase-reset of a potential hippocampal homologue. In contrast, techniques involving wavelet analysis and phase-locking statistics may be a more effective approach to determining phase-reset in humans. Current research has shown that phase-reset does contribute to event related potentials, particularly to early components such as the P1-N1 complex with peaks at ∼100 and ∼150 ms, respectively (Hanslmayr et al., 2007; Klimesch et al., 2004; Makeig et al., 2002), and the error related negativity (Luu et al., 2004; Yeung et al., 2007).

2.3. What is not FM-theta?

For the purpose of this review we shall exclude theta rhythms associated with pathology. These include: epilepsy (Ciganek, 1961; Mokran et al., 1971; Westmoreland and Klass, 1986); cerebral dysfunction in children (White and Tharp, 1974); Rett syndrome (Niedermeyer et al., 1997); during post-anoxic coma (Berkhoff et al., 2000); attention deficit hyperactivity disorder (Lazzaro et al., 1998; Mann et al., 1992); high pressure nervous syndrome (Okuda et al., 1988); and 50 Hz electrical stimulation of the anterior cingulate cortex (Talairach et al., 1973).

Some theta rhythms are clearly not fronto-central and so must be treated as separate from FM-theta—e.g. intracranial theta recorded from parietal and occipital sites during the Sternberg task (Raghavachari et al., 2006). However, theta rhythms recorded from other locations on the scalp and intra-cranially, that may be of relevance to FM-theta, will be discussed below where appropriate.

We shall exclude some of the normal, sleep related theta rhythms: the posterior low amplitude theta that occurs during drowsiness; the diffuse medium voltage theta that increases with increasing drowsiness (Janati et al., 1986); the 2–6 Hz sawtooth waves apparent fronto-centrally during REM sleep; and the apparent FM-theta that has been reported during NREM and stage 1 of sleep (Hayashi et al., 1987). These types of theta are generally different in both form and distribution to FM-theta.

2.4. What might be FM-theta?

There are some rhythms and frequency components that are in, or close to the theta band, that occur in normal participants and

that may or may not be FM-theta. Some of these rhythms are clearly fronto-central. Bursts (1–2 s increasing to 10 s-several minutes) of fronto-central theta rhythms (5–7 Hz) have been demonstrated during meditation (Banquet, 1973; Hebert and Lehmann, 1977). Hayashi et al. (1987) identified frontal-midline theta during specific sleep stages (mainly stage 1 and REM sleep) that were often associated with inner experiences with a distinct content. Takahashi et al. (1997) found similar characteristics between the FM-theta recorded during a mental task and that associated with drowsiness. Furthermore, participants who demonstrated FM-theta associated with drowsiness also demonstrated FM-theta while performing a task. This appears to create a paradox that FM-theta occurs in both a state of alertness or fixed concentration and drowsiness. However, it may be caused by an inhibitory mechanism that blocks out information when going to sleep or when trying to retain something in working memory or when focussing attention in meditation.

Conversely, these rhythms while appearing on the surface to be similar, may yet have quite distinct mechanisms. Therefore, with these rhythms, the issues are how far they share the psychological functional correlates and the electrographic and topographic features of conventional FM-theta. The key will be in designing experiments and methodologies that attempt to differentiate with more precision the electrographic features of different psychological processes such as working memory and meditative states.

For example, Shinomiya et al. (1994) conducted a study that revealed two distinct types of frontal-midline theta rhythm. Type 1 FM-theta was more prominent in healthy subjects, had a higher frequency, regular shape, lower voltage, and a shorter duration than Type 2 FM-theta that was more common in patients with epilepsy. Furthermore, Type 1 tended to spread bilaterally and anterior to Fz while the Type 2 theta was spread to posterior regions. Similarly, Gevins and Smith (1999) used a neural network algorithm to differentiate between a specific frontal-theta related to task demands and a diffuse theta associated with fatigue and hangover. In both these cases, then, quite careful parameter analysis is required to distinguish what appear to be functionally distinct but superficially quite similar rhythms.

One explanation of their being two "types" of FM-theta is that quite distinct circuits are involved in each case and, potentially, non-overlapping neural sources of the recorded rhythms. However, with rodent hippocampal theta, two pharmacologically distinct types have been identified (Bland, 1986)—a cholinergic-dependent type of theta occurring during immobility and one that is not cholinergically dependent that occurs when the animal is moving. These appear to involve the same frequency control circuits and, in essence, can been seen as the same fundamental "theta" that is "gated" by different modulatory inputs at different times (Gray and McNaughton, 2000). The two types of FM-theta, then, could involve the same core circuits, but released under different conditions—with the differing release conditions affecting which other brain regions are recruited.

Some theta rhythms have been attributed to 'emotional tension'. Mundy-Castle (1951, 1957) reported an emotionally elicited 5–6 Hz rhythm at various locations on the scalp. Sasaki et al. (1996a) reported fronto-parietal MEG theta rhythms elicited by emotional thoughts. These were of slightly higher frequency (6.3 Hz) than the MEG FM-theta reported in that study. With these rhythms it is not clear how far their frequency, topography or functional correlates can be identified with or distinguished from FM-theta.

Other possibly relevant rhythms are also found in infants and children. Generalised, high amplitude theta is a well known feature of the EEG of drowsy infants. Maulsby (1971) demonstrated an emotionally elicited posterior rhythm of 4 Hz, in a 9-month old

child old and Orekhova et al. (1999) demonstrated a frontal 3.6–4.8 Hz rhythm in 8–11 months old children during anticipation in a peekaboo game. Orekhova et al. (1999) also demonstrated a 5.2–6 Hz temporal rhythm that they suggested may have had an emotional substrate. Kugler and Laub (1971) reported a 4 Hz posterior rhythms in young children (>6 months) and 5–6 Hz frontal rhythms in older children (up to 6 years) during puppet shows or similar experiences. Theta rhythm can occur in the temporal and parietal regions in response to some form of external stimulation that causes the infant to orientate and direct attention (Kugler, 1973) and diminishes after a few seconds (Kugler and Laub, 1971). Kugler and Laub (1971) also noted that the theta tends to be more prominent in posterior locations in younger children and has a more anterior or central location later on. Also the frequency is typically 4 Hz in younger children and 5–6 Hz in older children. A frontal-midline 6–7 Hz theta rhythm is a recognised feature in the EEG of awake children (Niedermeyer, 1987). These results raise the question of how far adult FM-theta and its variations across subjects represent maturational restriction of the occurrence of theta and how far the theta components in children can be seen as distinct from adult FM-theta and like the theta components that are seen in adult pathology.

In summary, there are a variety of psychological states that are associated with theta recorded at frontal electrode sites. When attempting to distinguish FM-theta from other EEG features, it is important to note that some abnormal theta rhythms and some normal rhythms identified in children are almost indistinguishable from FM-theta in terms of the waveform characteristics and topography outlined in Section 2.2.1. We will return to some of these rhythms in the discussion.

2.5. Electrographic features of hippocampal theta

The electrographic features of FM-theta described above lie within the domain of expected features of hippocampal theta. Hippocampal theta has been difficult to isolate in humans. It is unlikely that hippocampal theta would be projected directly to scalp electrodes by volume conduction, and therefore we are generally restricted to the rare occasions where electrodes are placed directly into the human hippocampus in subjects with severe underlying pathology. Those investigations have indicated a range of human hippocampal theta frequencies. Sano et al. (1970) applied 100 Hz stimulation to the posterior hypothalamus in patients undergoing surgery and often observed theta (6–7 Hz in the figure presented as an example) in electrodes placed in the hippocampus. Halgren et al. (1978) identified a behaviour modulated 5–6 Hz rhythm in the hippocampus of a subject undergoing monitoring for epilepsy surgery. This 5–6 Hz rhythm desynchronised during certain behaviours, but the authors suspected that it was abnormal. Arnolds et al. (1980a) identified a behaviour-modulated 3–4 Hz hippocampal rhythm. Isokawa-Akesson et al. (1987) recorded extracellular single-unit activities from the anterior hippocampus through fine platinum microelectrodes. They investigated 23 subjects, and analysed firing rates using autocorrelation analysis and inferred clear rhythmic components in the range 6.7–17 Hz.

More recently, MEG and signal processing techniques have been used in attempts to study hippocampal theta in normal subjects (It should be noted that the capacity of MEG to do so is controversial.). Tesche (1997) used a full head MEG array on normal subjects during mental arithmetic and passive picture viewing and identified complex activity, attributed to the hippocampus, with spectral features with components below 12 Hz, including some task dependent peaks. Tesche and Karhu (2000) have since reported a task-specific 7 Hz theta component in signals suggested to originate in the hippocampi of normal subjects.

Theta, when recorded directly from the human hippocampus, is generally identified using signal processing and is not always clearly apparent in the raw EEG (but see, e.g. Sano et al., 1970). This is in contrast to hippocampal theta in non-primates, particularly rodents, usually used to study hippocampal theta. This may be due to underlying pathology, electrode location, activation procedures, conformation of the hippocampal cell layers or a consequence of the broad range of ongoing activity that occupies the human hippocampus. Precise electrode location affects the amplitude of theta markedly in rodents (Robinson, 1980) and is clearly one of the most important variables to assess in future experiments. However, it should be noted that theta appears as difficult to record in other primates as in humans (Crowne et al., 1972; Stewart and Fox, 1991) and also can require the use of signal processing techniques to demonstrate it (Tsujimoto et al., 2006).

3. Localization

3.1. Localization of FM-theta

While many studies of FM-theta use a small number of electrodes concentrated around the region of interest, several investigators have attempted to localise the source of FM-theta with high resolution surface EEG recordings or with paired EEG/MEG recordings. There are likely to be multiple generators of theta rhythm recorded in the human EEG (Raghavachari et al., 2006). To date several brain regions have been implicated as potential sources of FM-theta.

FM-theta is generally maximal at, or just anterior to, Fz with little posterior propagation (Yamaguchi et al., 1990b); but its maximum amplitude can shift within 3 cm around Fz, even within a single subject (Ishihara et al., 1981). The localised distribution of FM-theta power indicates that it probably originates from a source on or near the frontal midline. It should be remembered, however, that source analysis based on scalp EEG is difficult because of the inverse problem (Koles, 1998). For example, the N100-P200 complex for late auditory evoked potentials has a midline maximum that was initially thought to originate from the frontal lobes or widespread, diffuse sources (e.g. Picton et al., 1974) but it is now thought to be localised to a group of bilateral sources in the auditory cortices (Scherg et al., 1989; Scherg and Von Cramon, 1985).

Sasaki et al. (1994b) were the first to look for a source for FM-theta using synchronised MEG/EEG and suggested that it was generated by multiple bilateral sources within the frontal lobes and they suggest that the midline maximum is due to vector summation (Sasaki et al., 1996c). The MEG studies by Sasaki (Sasaki et al., 1994b, 1996c) have sometimes demonstrated an asymmetry in the MEG maxima, with the right fronto-central area having a clearly higher signal.

Inouye et al. (1994b) noted a lateral to medial potential flow of FM-theta in areas in front of Fz with a medial to lateral potential flow in areas behind Fz during the performance of the Uchida-Kraepelin task. It was also suggested that FM-theta moves in a circular clockwise motion in the left frontal regions and anticlockwise in right frontal regions. Iramina et al. (1996) suggested a single midline dipole source, but questioned the validity of that model. Ishii et al. (1999) used MEG techniques and proposed sources in the bilateral medial prefrontal cortices, including anterior cingulate cortex (ACC). They pointed out that if large areas of frontal cortex were involved in generating FM-theta then point source dipole analysis may not be appropriate. They also suggested that the thalamus might be driving FM-theta. Asada et al. (1999) used EEG combined with MEG and proposed two sources in the regions both of the prefrontal-medial superficial

cortex and ACC. They suggested that these regions were alternately activated during one FM-theta cycle. Gevins et al. (1997) used high spatial resolution EEG in conjunction with Magnetic Resonance Imaging (MRI) and suggested a medial prefrontal source in the region of the anterior cingulate but noted that because of the anatomy of this structure it was not possible to determine if this was or was not bilateral. Similarly, Onton et al. (2005), using a dipole source model, localised FM-theta to the approximate region of the dorsal ACC. Sauseng et al. (2007) used low-resolution electromagnetic tomography analysis (LORETA) to study the source of FM-theta during a motor working memory task. The LORETA revealed the source of FM-theta during this task to be the anterior cingulate gyrus and the cingulate motor area. Finally, Tsujimoto et al. (2006) attempted to localise FM-theta in monkeys while performing a task whereby a lever had to be lifted for a certain period before a reward was given. Releasing the lever resulted in a waiting period. Increased theta located in the rostral ACC and prefrontal cortex occurred prior to and following hand-movements. Rewarding the hand movement resulted in a secondary gain in theta amplitude. Although this finding is perhaps consistent with the human data it is unclear whether monkey and human frontal-midline theta are homologous.

All of these analyses suggest a frontal lobe/ACC source or sources for FM-theta. This is consistent with the ACC being connected to a number of different brain regions and involved in a range of cognitive and emotional functions such as motivation, decision making, processing information, and attention (Devinsky et al., 1995; Pardo et al., 1990; Posner and Petersen, 1990; Wang et al., 2005). However, this is not entirely consistent with the recent findings of Kahana et al. (1999). They identified clear 4–8 Hz rhythms from subdural electrode arrays recording from the superficial cortex in three subjects during virtual maze navigation. This type of task can generate superficial FM-theta (video games and a simulated driving task have been used to elicit FM-theta). However, they had no surface electrodes and so the relation of their recordings to conventional FM-theta is unclear. They found theta from recordings made by electrode contacts over broad areas of cortex including the temporal lobe, the parietal lobe, the inferior frontal gyrus and the central sulcus. Theta appeared in discrete bursts of 1–2 s and occurred more frequently in more complex mazes and during recall trials. Given the nature of intracranial EEG (a very high amplitude signal recorded directly from the cortex with no intervening layers), it is likely that the recorded rhythms originated from sources near to the recording electrodes, and are probably not attributable to volume conduction. FM-theta, then, may have a regular superficial location at frontal sites not because of a frontal generator but because of the way that multiple subdural generators combine to produce the superficial field.

Cortical theta could be linked to theta generated within the hippocampus. Correlations in the occurrence of theta between hippocampal and neocortical sites have been noted during a virtual navigation task (Ekstrom et al., 2005). Furthermore, Fell et al. (2003) found 1–19 Hz coherence between hippocampal and adjacent rhinal cortex during a declarative memory task. However, other studies have not demonstrated a clear link between theta recorded in the hippocampus and cortical regions in humans (Cantero et al., 2003; Raghavachari et al., 2006) also see (Kahana et al., 2001). In rats, frontal cortex and hippocampus often show independent theta activity of different frequencies but, during exploratory activity, can show coherence with frontal areas becoming locked to the hippocampus (Young and McNaughton, 2008). This observed behaviour-dependence could account for the variation in findings in the human studies.

3.2. Localization of hippocampal theta

Human hippocampal theta has not been definitively localised to sources within the hippocampus. Halgren et al. (1978) identified theta from all electrode contacts in the hippocampus of their subject and it was most prominent in the contacts in the posterior hippocampal gyrus. Arnolds et al. (1980a) identified a 3–4 Hz rhythm in the area of the pes hippocampi. Isokawa-Akesson et al. (1987) identified a clear rhythm of 6.7–17 Hz in the anterior hippocampus. Sano et al. (1970) identified a 5.5–6.0 Hz in the right hippocampus. However, current source density analysis of the type required to determine source locations has not been carried out (and for ethical reasons is unlikely to be carried out).

In animal studies, hippocampal theta is usually recorded from local fields in the CA1 and dentate layers of the hippocampal formation. Theta rhythm has also been recorded from area CA3 (Villarreal et al., 2007), perirhinal cortex (Bilkey and Heinemann, 1999), the cingulate cortex (Colom et al., 1988; Talk et al., 2004), entorhinal cortex (Dickson et al., 1995, 1994), hypothalamus, cortical structures, and amygdala (Seidenbecher et al., 2003). Furthermore, rat hippocampal theta is strongly linked to phase-locked theta rhythms in the posterior cortex (Colom et al., 1988), cingulate cortex (Feenstra and Holsheimer, 1979), and can sometimes be linked to phasic single cell firing in frontal cortex (Siapas et al., 2005). Furthermore, the hippocampus receives a number of inputs from the hypothalamus and medial septum/diagonal band complex that are involved in the modulation of theta (Kirk, 1998).

The lack of reports of strong frontal theta rhythm (as opposed to phasic cellular activity) in rodents suggests that human, superficially recorded, FM-theta is not likely to be related to hippocampal theta. However, it should be remembered that both the cingulate cortex (Colom et al., 1988; Talk et al., 2004) and entorhinal cortex (Dickson et al., 1994) can generate theta and that the hippocampus has strong connections to the frontal cortex (Miller, 1991). FM-theta could, then, be a reflection of rhythmic hippocampal cellular activity that does not produce a superficially recordable hippocampal rhythm but does entrain frontal cells and produce, at least sporadically, rhythmic activity that is coherent with hippocampal activity—and there is preliminary direct evidence that this is the case (Young and McNaughton, 2008). Theta recorded above temporal cortex could, likewise, result from entorhinal theta that is not accompanied by a recordable hippocampal rhythm. This would be similar to the entrainment of hippocampal theta frequency by septal pacemaker cells. Indeed, and more generally, it has been argued that the function of theta activity (in populations of neurons) is to integrate or coordinate activity across a distributed system that may have elements in neocortex, and diencephalon as well as the hippocampus (Bland, 1986; Bland and Oddie, 2001; Kirk and Mackay, 2003).

It is also, of course, possible that frontal rhythmic activity could occur completely independently of the hippocampus. Certainly, where FM-theta is a different frequency from theta activity concurrently recorded from other sites then one or both of these must be independent of the hippocampus–activity throughout which is generally coherent.

4. Prevalence and age distribution

Some investigators recruit or analyse data only from those subjects that demonstrate reliable FM-theta. For example, restricting analysis to Fz and cases where FM-theta had "(1) rhythmical-sinusoidal configuration; (2) markedly higher amplitude as compared to background activity, and (3) duration exceeding 1 s (Mizuki et al., 1980, p. 346)". Furthermore, reports on the presence of FM-theta may differ depending on what participants are required to do during the experiment. In fact, not all people display this phenomenon in scalp recorded EEGs (Table 1) and there appears to be an age distribution with FM-theta being most common in young adults, with the incidence decreasing significantly after about 30 years of age. Although reaching a peak in young adults, increases in 4–5 Hz theta over frontal and prefrontal regions were noted during a peekaboo game that involved both internal (or anticipatory) and external attention in 7–8-month-old infants (Stroganova et al., 1998). Activity at 5–6 Hz was noted to increase only during the internal attention component. At the other extreme, in an older sample aged ∼69 years, FM-theta did not increase with working memory task demands (McEvoy et al., 2001). Why this age-related peak occurs is unclear, but in some ways this mimics the prevalence and age distribution of scalp recorded mu rhythm (a rhythm in the alpha range that is maximal over somatosensory cortex and shows suppression during contralateral movement) which is identified in about 8% of the population with a peak of about 13.8% in 10–20 years olds (Niedermeyer, 1987). The opposite pattern is noted with alpha rhythm. It is interesting to note, however, that when MEG or

Table 1
Prevalence and age distribution of FM-theta

Investigators	Age range	Sample size	FM-theta presence	Number of subjects displaying FM-theta	
Asada et al. (1985)	19–23 years	191	Yes	71	37%
Cummins and Finnigan (2007)	18–27 and 60–80 years	14n per group	Greater increase with task difficulty in younger group	–	–
Ishihara and Yoshi (1972)	18.3 years (mean)	115	Yes	60	52%
McEvoy et al. (2001)	21 years	10	Increased with task difficulty	–	–
	47 years	10	Increased with task difficulty	–	–
	69 years	10	Decreased with task difficulty	–	–
Mizuki et al. (1980)	20–26 years	30	Yes	19	63.3
Mizuki et al. (1984)	18–23 years	40	Yes	12 (day 1), 18 (day 2), 22 (day 3)	30 (day 1), 45 (day 2), 55 (day3)
Nakagawa (1988)	–	24	Yes	16	67%
Nakamura and Mukasa (1992)	20–23 years	24	Yes	12	50
Takahashi et al. (1997)	18–25 years	34	–	1	3%
Yamaguchi et al. (1981)	18–25 years	320	Yes	124	39%
Yamaguchi et al. (1985)	18–28 years	513	Yes	218	43%
Yamaguchi et al. (1990a,b)	18–28 years	677	Yes	293	43%
	30–59 years	85	Low	8	9%
	60–79 years	73	Low	6	8%

signal processing techniques are used, the reported incidence of mu significantly increases (Kuhlman, 1978; Pfurtscheller and Aranibar, 1978; Tiihonen et al., 1989) and it is now suggested that mu is a normal rhythm in almost all, if not all subjects. Thus, it is probably only the expression of that rhythm in visually inspected scalp EEG that is maximal during adolescence. The same may prove true for FM-theta. In studies where a frontal-midline theta component has been identified using signal processing techniques and paradigms known to evoke FM-theta rhythms, the prevalence is high (Gevins et al., 1997; Smith et al., 1999). FM-theta was more prevalent in the 13–15 years age range in patients with various diagnoses including epilepsy, brain damage, behavioural disorders, autonomic disorders, headache, and other problems (Palmer et al., 1976).

There is reasonable evidence that the occurrence of FM-theta is different for different age groups. However, FM-theta has a number of other features that may be worth examining at different age levels. It has been found that, during the performance of a passive auditory and oddball task, adults have stronger phase-locking in the theta range recorded at Fz, Cz, and Pz. However, the phase locking for the early theta component was not as pronounced at Fz and Pz. Furthermore, adults tended to show a greater increase in the amplitude of theta from pre- to post-stimulus presentation than children. Finally, children had significantly higher theta amplitudes than adults (Yordanova and Kolev, 1997b). Greater phase-locking and amplitude increases have also been noted in middle aged compared to young adults (Yordanova et al., 1998). Further studies still need to examine what functional or performance variables coincide with these changes in FM-theta with age.

5. Behavioural modulation

5.1. Events that modulate FM-theta

Theta rhythmicity can be present as a tonic background present over considerable areas of the scalp for considerable periods of time. However, it can also occur in a phasic fashion, showing a clear increase in power linked to the occurrence of either internal or external stimuli. Preliminary attempts to assign functions to theta (both in the older rat hippocampal literature and in the more recent human frontal literature) have focussed on the correlation between the phasic elicitation of theta (or changes in its power or frequency) and specific stimuli or behaviours. However, in interpreting this literature, it should always be remembered that correlation does not prove cause. In the case of rat hippocampal theta, both its elicitation and highly significant correlations with power and frequency occur in relation to behaviours (such as running down a straight alley) that are unaffected even by total removal of the hippocampus. It follows that the occurrence of theta will often be a sign of some function being executed in some part of the brain—but its occurrence at a particular site may indicate no more than the receipt by that site of an efference copy of the activity elsewhere. It may be important for function in the structure generating it only on that subset of occasions when that structure produces functional output.

Arellano and Schwab (1950) were the first to report the presence of theta recorded from frontal electrodes in a young man during the performance of arithmetic problems. Since then a number of behaviours and cognitive processes such as working memory, spatial navigation, episodic memory, and meditation have been shown to elicit FM-theta. Typically, some form of difficult sequential mathematical exercise such as the Uchida-Kraepelin exercise of repeated addition is employed to elicit FM-theta. Table 2 lists the activation procedures used to elicit FM-theta in those studies. The common feature traditionally cited for these tasks is non-specific, focused or sustained attention or concentration, or resistance to intrusion. However, a number of other task components such as encoding, retrieval, performance, and practice have been shown to influence FM-theta activity. Ishihara and Yoshi (1972) claimed that the quantity of FM-theta was related to the amount and speed of mental work and that it tended to appear

Table 2
Results from papers demonstrating modulation of frontal midline theta rhythm during the performance of a behavioural task

Investigators	FMTR			FMTFC	Task	Field	Max
	Hz	Amp μv	Duration				
Arellano and Schwab (1950)	–	–	–	Not specified	Abstractive mental work (arithmetic problems)	Anterior to vertex, frontocortical	–
Aftanas and Golocheikine (2001) (res)	–	–	–	3.77–7.54	Meditation (internalised attention)/blissful state	Frontal	AFz, Fz
Asada et al. (1999) (res)	6.4	~50	~3 s	–	Serial addition, serial subtraction, recollection of Kanji characters, attention to slow breathing	Frontocentral (vm, EEG, MEG)	Fz, Fpz
Bastiaansen et al. (2002b) (res)	–	–	–	3.9–7.9 Hz dec (IBP)	Spatial delayed response task	Frontal	–
Bastiaansen et al. (2002a) (res)	–	–	–	Theta-IAF (IBP)	Sentence processing	Frontocentral temporo-parietal	–
Banquet (1973) (res)	5–7	Up to 100	1–2 s	4–7 Hz	Transcendental meditation	Frontal	F3
Brazier and Casby (1952) (res)	6	~50	>1 s	–	Mental calculation	?vertex	?vertex
Brookings et al. (1996) (res)				4.3–7.8 Hz	Air traffic simulator	Frontal	Fz
Burgess and Gruzelier (1997) (res)	–	–	–	–	Word recognition memory task	Frontocentral	–
Caplan et al. (2003) (res)	–	–	–	4–8 Hz	Virtual visual-spatial navigation	Frontal?	Variable
Chung et al. (2002) (res)	–	–	–	5–7 Hz	Visuo-spatial N-back task	Frontal	AFz
Cohen et al. (2007) (res)	–	–	–	4–8 Hz	Probabilistic reinforcement learning task	Frontal	Fz
de Araújo et al. (2002) (res)	–	–	–	3.7 Hz	Virtual visual-spatial navigation	Frontal to posterior propogation?	–
Deiber et al. (2007) (res)	–	–	–	4–8 Hz	Verbal N-back task	Frontal	Fz
Dietl et al. (1999) (res)	–	–	–	4–7.5 Hz	Repetitive electric stimulus	Frontal	Fz
Doppelmayr et al. (1998) (res)	–	–	–	Theta-IAF?	Episodic recognition memory task	Frontal	–
Ekstrom et al. (2005) (res)	–	–	–	4–8 Hz	Virtual visual-spatial navigation	Frontal	–
Fernández et al. (2000) (res/ill)	–	–	–	5.46/6.24 Hz	Sternberg verbal working memory	Frontal	–
Gevins et al. (1979a) (res)	–	–	–	4–7 Hz	Koh's block design	Frontal	

Table 2 (*Continued*)

Investigators	FMTR Hz	Amp μv	Duration	FMTFC	Task	Field	Max
Gevins et al. (1979b) (res)	–	–	–	4–7 Hz	Koh's block design, mental paper folding	Frontal	–
Gevins et al. (1997) (res)	6 (5–7)	'high'	0.5–2 s	5–7 Hz	Visuo-spatial and verbal N-back task	Frontocentral (vm)	Afz
Gevins et al. (1998) (res)	–	–	–	4–7 Hz	Visuo-spatial and verbal N-back task	?Frontocentral	Fz
Gevins and Smith (1999) (res)	–	–	–	5–7 Hz	Visuo-spatial N-back task	Frontal	Fz
Gevins and Smith (2000) (res)	–	–	–	5–7 Hz	Visuo-spatial N-back task	Frontal	Fz
Gevins et al. (2002) (res)	–	–	–	5–7 Hz	Visuo-spatial N-back task	Frontal	Fz
Grunwald et al. (1999) (res)	–	–	–	4–8 Hz	Haptic exploration	Frontocentral	
Grunwald et al. (2001b) (res)	–	–	–	4–8 Hz	Haptic exploration	Frontocentral	Fz
Harmony et al. (1999) (res)	–	–	–	3.9 and 5.46 Hz	Mental calculation	Frontal	–
Harmony et al. (2001) (res)	–	–	–	7.8 Hz	Figure categorization	Prefrontal, anterior cingulate	AFz
Hashimoto et al. (1988) (ill)	7	~75	1–5 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Ilan and Gevins (2001) (res) (ill)	–	–	–	5–7 Hz	Visuo-spatial N-back task	Frontal	Fz
Inanaga et al. (1983) (ill)	5	~50	1–3 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Inouye et al. (1994a) (res)	6.5	100–200	>5 s	–	Uchida-Kraepelin	Frontocentral	Fz
Inouye et al. (1994b) (res)	6.5	100–200	>5 s	–	Uchida-Kraepelin	Frontocentral	Fz
Iramina et al. (1996) (res)	–	–	1–5 s	6–7 Hz	Mental calculation	Frontocentral (EEG/MEG)	–
Ishihara and Yoshi (1972) (ill)	6.5	>100	>7 s	–	Uchida-Kraepelin	Frontocentral	Fz
Ishii et al. (1999) (ill)	6	~50	>10 s	–	Serial sevens, serial addition, powers of 3	Frontocentral (vm, MEG)	Fz
Jensen and Tesche (2002) (res)	–	–	–	7–8.5 Hz	Sternberg memory task	Frontocentral (MEG)	–
Kahana et al. (1999) (ill)	4–8	100–200	1–2 s	–	Virtual visual-spatial navigation	Diffuse? (iEEG)	–
Katayama et al. (1992) (res)	5–7.5	~50	2 s	–	Music, playing and imagining	Frontocentral	Fz
Klimesch et al. (1994) (res)	–	–	–	3.9–7.4 Hz ERD/ERS	Episodic memory task	Frontal	–
Klimesch et al. (1996b) (res)	–	–	–	4.69–6.69 Hz, 6.69–8.69 Hz ERD/ERS	Implicit episodic memory task	Fronto-central	–
Klimesch et al. (1997) (res)	–	–	–	4.3–6.3 Hz ERD/ERS	Episodic memory task	Frontal	–
Klimesch et al. (2001) (res)	–	–	–	Theta-IAF? ERD/ERS	Episodic memory task	Frontal	Fz
Krause et al. (2000) (res)	–	–	–	4–6 Hz, 6–8 Hz ERD/ERS	Verbal (visual) N-back task	Anterior	–
Krause et al. (2001) (res)	–	–	–	4–6 Hz, 6–8 Hz ERD/ERS	Modified auditory Sternberg task	Anterior	–
Krause et al. (2002) (res)	–	–	–	4–6 Hz, 6–8 Hz ERD/ERS	Modified auditory Sternberg task	Fronto-central	–
Krause et al. (2006) (res)	–	–	–	4–6 Hz ERD/ERS	Visual > auditory stimuli in a lexical decision making task	Frontal (diffuse)	–
Kubota et al. (2001) (res) (ill)	6–7	–	1–1.5 s	4–8 Hz	Zen meditation	Frontal	Fz
Laukka et al. (1995) (res)	–	–	–	4–7 Hz	Simulated car driving task	Frontal	Fz
Laukka et al. (1997) (res)	–	–	–	4–7 Hz	Simulated car driving task	Frontal	Fz
Lehmann et al. (1993) (res)	–	–	–	1–7.5 Hz	Abstract thinking	Frontal	–
Martin (1998) (res)	–	–	–	4–7 Hz	Olfactory stimulation	Frontal	Fz
MacKay et al. (2001) (abstract)	–	–	–	4–7 Hz	Visual-spatial navigation/ Sternberg memory task	Frontal	–
McEvoy et al. (2000) (res)	–	–	–	4–7 Hz	Visuo-spatial N-back task	Frontal	Fz
McEvoy et al. (2001) (res)	–	–	–	4–7 Hz	Visuo-spatial N-back task	Frontal	–
Missonnier et al. (2006) (res)	–	–	–	4–7.5 Hz	Verbal (visual) N-back and detection task	Fronto-central	–
Mizuki et al. (1980) (ill) (res)	6	~75	1–7 s (20.5–110 s)	–	Uchida-Kraepelin	?Frontocentral	Fz
Mizuki et al. (1983)[a] (ill)	6	~75	1–4 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Mizuki et al. (1984) (res)	?	–	3–10 s	–	Uchida-Kraepelin	Frontocentral	Fz
Mizuki et al. (1986) (ill)	6	~75	1–4 s	–	Uchida-Kraepelin	Frontocentral	Fz
Mizuki et al. (1989) (res)	–	–	–	4.5–7.5 Hz	Uchida-Kraepelin	Frontocentral	Fz
Mizuki et al. (1994) (ill)	6.5–7	~75	1–4 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Mizuki et al. (1996) (ill)	5.0–7.5	~75	>1 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Mizuki et al. (1997) (ill)	5.0–7.5	~75	>1 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Mizutani et al. (1985a) (abs)	–	–	–	6–7 Hz	Uchida-Kraepelin	?Frontal	?Fz
Mizutani et al. (1985b) (abs)	–	–	–	6–7 Hz	Uchida-Kraepelin	?Frontal	?Fz
Mölle et al. (2002) (res)	–	–	–	4–8 Hz	Intentional learning of words	Fronto-temporal	–
Moore et al. (2005) (res) (ill)	–	–	–	4–6 Hz	Continuous go/no-go task	Frontocentral	?Fz
Nakamura and Mukasa (1990) (ill)	6–7	~75	2–3 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Nakamura and Mukasa (1992) (ill)	6–7	~75	2–3 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Nishikori et al. (1985) (abs)	–	–	–	?	Mental calculation	?Frontal	?Fz
Onton et al. (2005) (res)	–	–	–	5–7 Hz	Verbal (visual) Sternberg memory task	Frontal	Fz
Pellouchoud et al. (1999) (res)	–	–	–	6.5 Hz	Watching and playing video game	Frontocentral (vm)	Fz

Table 2 (*Continued*)

Investigators	FMTR			FMTFC	Task	Field	Max
	Hz	Amp μv	Duration				
Peterson and Thaut (2002) (res)	–	–	–	4–8 Hz	Visual continuous match to sample	Frontal	F3/F4
Raghavachari et al. (2001) (res)	–	–	–	4–9 Hz	Sternberg working memory task	?Frontal (iEEG)	–
Sarnthein et al. (1998) (res)	–	–	–	4–7 Hz	Working memory task	?Frontocentral	
Sasaki et al. (1994b) (res)	–	–	–	5–7 Hz	Successive subtraction, musical imagination	Frontocentral (MEG)	–
Sasaki et al. (1996a) (res)	–	–	–	5–7 Hz	Successive subtraction, musical imagination	Frontocentral (MEG)	–
Sasaki et al. (1996b) (res)	–	–	–	5–7 Hz	Mental calculation/abstract thinking	Frontal (MEG)	–
Sasaki et al. (1996c) (ill)	6.3	~75	>4 s	–	Powers of 3	Frontocentral (EEG, MEG)	Fz
Sauseng et al. (2004) (res)	–	–	–	4–7 Hz	Object visual working memory	Fronto-parietal	–
Sauseng et al. (2006) (res)	–	–	–	4–7 Hz	Task switching working memory	Fronto-posterior	
Sauseng et al. (2007) (res)	–	–	–	4–7 Hz	Complex sequential finger movements	Frontal	–
	–	–	–	3–7 Hz	Verbal/non-verbal Sternberg task	Frontocentral	Fz
Sederberg et al. (2003) (res)	–	–	–	4–8 Hz	Delayed recall task	Fronto and right-temporal (iEEG)	–
Shinomiya et al. (1994) (res)	6.63	54	1.97 s	–	Spontaneously occurring	Frontocentral	Fz
Smith et al. (1999) (res)	–	–	–	6.5 Hz	Visuo-spatial working memory paradigm and video game	Frontocentral (vm)	Fz
Smith et al. (2001) (res)	–	–	–	6–7 Hz	Flight simulator	Anterior/frontal	Fz
Stam et al. (2002) (res)	–	–	–	2–6 Hz	Pictorial working memory retention	Fronto and posterior-temporal, parietal, occipital	–
Suetsugi et al. (1998) (res)	5.0–7.5	~75	>1 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Suetsugi et al. (2000) (res)	5.0–7.5	~75	>1 s	–	Uchida-Kraepelin	?Frontocentral	Fz
Takahashi et al. (1997) (ill)	6	~50	1–2.5 s	–	Uchida-Kraepelin	Frontocentral	Fz
Wilson et al. (1999) (res)	–	–	–	4.3–7.8 Hz	Working memory	Frontal	–
Yamaguchi et al. (1990a) (abs)	–	–	–	6–7 Hz	Mental work	Frontal-midline	–

FMTR implies FM-theta rhythm as identified from EEG records such as figures and descriptions, FMTFC implies FM-theta frequency components as identified using signal processing, 'res' implies data obtained from results section. 'ill' implies data measured from illustrative example, 'abs' implies abstract. Theta-IAF implies theta adjusted according to individual peak alpha frequency. 'wm' implies working memory. '?' implies uncertainty because of insufficient data. '(vm)' implies that field is estimated from a voltage map. '(EEG)' implies that field is estimated from an illustration of raw EEG, iEEG implies intracranial EEG, MEG implies magnetoencephalography ERD implies event related desynchronization, ERS implies event related synchronization, IBP implies induced band power. Max indicates a clear focal increase in FM-theta, whereas left blank indicates not enough data.

^a Same patients as Inanaga et al. (1983) paper.

clearly if the task was performed smoothly, but it disappeared if the calculation rate decreased. A similar finding was reported for the MEG frontal-mental theta (Sasaki et al., 1996a, 1994a). Mizutani et al. (1985b) reported that task performance improved during periods of FM-theta, when compared to periods when no FM-theta was present. FM-theta has also been noted to increase with practice during video game playing (Smith et al., 1999). Mizutani et al. (1985a) reported an increase in performance speed of a mathematical task during periods when FM-theta was present. In these tasks FM-theta is usually elicited in discrete bursts of fairly homogeneous frequency that last up to several seconds, possibly with an underlying period of around 40–50 s (Mizuki et al., 1980).

In our review of this literature, we will first explore the simplification that there could be an isolated unitary frontal-midline theta responsible for a variety of distinct behavioural processes. Across behavioural studies the specific temporal, topographic, and frequency components of theta activity vary. There is also evidence that theta activity at the fontal midline is coupled with activity at other brain areas, not only at theta frequencies (Sarnthein et al., 1998) but also in other frequency bands such as gamma (Schack et al., 2002). The EEG studies discussed below suggest only that FM-theta has some kind of mnemonic or cognitive function but they neither make this certain, nor clearly identify a specific function that can be attributed to it; nor show whether there is just one functional type of FM-theta. Experiments thus need to be carefully designed to tease out functions of theta. The following section examines some of the tasks that have been related to FM-theta activity. A later section will discuss the relationship between FM-theta and activity at other brain sites.

5.2. Working memory studies

Working memory is the ability to temporarily hold and manipulate a limited amount of information in immediate awareness and is often necessary in order to produce a correct response (Baddeley, 1986; Baddeley and Hitch, 1974). Baddeley has proposed that working memory is comprised of a central executive component, a visual-spatial scratchpad, and a phonological loop. The Sternberg task (Sternberg, 1966) and the N-back task are frequently used to study working memory. The Sternberg task involves the presentation of a stimulus list capable of being held in working memory, followed by a delay period before the presentation of a probe stimulus. The participant has to indicate whether or not the probe was presented in the stimulus list. The N-back task involves the continuous presentation of items, whereby the participant has to indicate whether each item is the same or different from an item presented previously. The following section outlines the different tasks and parameters shown to elicit or produce changes in FM-theta.

A clear relationship exists between working memory tasks and frontal-midline theta (4–8 Hz) spectral activity. Both the Sternberg task (Jensen and Tesche, 2002; MacKay et al., 2001; Onton et al., 2005) and the N-back task (Deiber et al., 2007; Gevins and Smith,

1999; Gevins et al., 1998, 1997, 2002; Krause et al., 2000; Missonnier et al., 2006; Smith et al., 1999) have been shown to elicit FM-theta; as has relational list learning (Caplan and Glaholt, 2007) and word-colour association (Summerfield and Mangels, 2005). In addition, other tasks with a proposed working memory component such as "mental rotation, Koh's block design, serial addition, substitution of letters with subsequent word recognition" (Gevins et al., 1979a,b), Uchida-Kraepelin task (Ishihara and Yoshi, 1972), flight simulation tasks (Smith et al., 2001), air-traffic control tasks (Brookings et al., 1996), videogame playing (Pellouchoud et al., 1999; Smith et al., 1999), the playing of complicated pieces of music, or the imagining of that music (Katayama et al., 1992), and complex and novel motor sequence tasks (Sauseng et al., 2007) also produce theta at frontal locations. The working memory tasks shown to increase FM-theta involve a number of different sensory modalities including motor (Sauseng et al., 2007), verbal (Gevins et al., 1997; Krause et al., 2000), auditory (Krause et al., 2001), and visual-spatial (Gevins and Smith, 1999; Gevins et al., 1997) information. Gevins et al. (1997) found that there were no differences in the amount of FM-theta produced by either a verbal or visual-spatial task.

Perhaps the most often reported relationship shows an increase in the amount of 4–7 Hz FM-theta with increasing working memory load, task difficulty, or mental effort (Gevins and Smith, 1999, 2000; Gevins et al., 1998, 1997; Grunwald et al., 1999; Jensen and Tesche, 2002; Laukka et al., 1995; McEvoy et al., 2000; Sauseng et al., 2007; Smith et al., 2001; Yamaguchi et al., 1990b). For example, Jensen and Tesche (2002) using a 122 channel, whole head, MEG array during a Sternberg paradigm found that FM-theta in the range of 7–8.5 Hz increased in power as a function of the memory set size and persisted during retention and comparison of the probe to the memory set. Consistent with this, Onton et al. (2005) demonstrated an increase in 5–7 Hz theta activity at Fz with an increase in working memory load during the Sternberg task. Interestingly, the increase in FM-theta with working memory load was the result of a small fraction of trials showing a large increase in activity rather than a modest increase on most trials. This has important implications both for methodology and interpretation.

Recent attempts have also been made to separate out components of working memory in the EEG. Missonnier et al. (2006) investigated 4–7.5 Hz ERS during a verbal N-back 1 task, an N-back 2 task, a detection task, and a passive fixation task that each involved the visual presentation of verbal stimuli. There was a clear increase in 4–7.5 Hz ERS following stimulus presentation during each of the tasks that had a shorter latency to peak at posterior compared to anterior electrode sites. At frontal electrode sites the amplitude of the peak was greatest during the detection, followed by the N-back 1, N-back 2 and then passive task. The greatest amplitude occurred during the attention task which was also significantly greater than the 4–7.5 Hz peak that occurred during the N-back 2 and passive conditions at both central and frontal electrodes sites. Thus, theta observed during such tasks may reflect the allocation of attentional resources related to working memory. Missonnier et al. (2006) suggested that the lower level of spectral power observed during the N-back 2 condition may reflect the allocation of resources to other aspects of the working memory task. Similarly, Deiber et al. (2007) found that 4–8 Hz energy was greater following stimulus presentation in the attentional and N-back tasks compared to the passive task at frontal electrode sites. Deiber et al. (2007) also reported on theta components recorded at Fz to examine components of working memory using a similar paradigm. Greater 4–8 Hz energy was noted during the delay period on no-response trials during the verbal N-back 2 compared to N-back 1 and detection tasks at frontal electrodes. Transient energy, occurring earlier in the delay period, was

reduced in the passive task but was similar for the N-back and detection tasks. These results suggest that earlier transient components of theta at frontal sites may be important for attention-related functions whereas later sustained components are important for working memory. This is consistent with Sauseng et al. (2007) who suggested that frontal-midline theta per se may reflect the activity of an attentional system while frontal theta coherence with theta at other brain regions may be involved in dealing with working memory demands such as the executive control and integration of information.

FM-theta has also been related to additional performance parameters. Gevins et al. (1997) found that reaction speed decreased, accuracy increased and the FM-theta response increased near the end of practice. Smith et al. (1999) demonstrated that the amount of FM-theta increased over time and over sessions in both an N-back experiment and a spatial navigation videogame. Fernández et al. (2000) looked at theta in relation to correct and incorrect answers during a verbal (Sternberg paradigm) working memory task, spatial working memory task, and during calculation of mathematical sums. Prior to correct responses made on the verbal working memory task they noted a statistically significant increase in 5.46 Hz EEG power recorded from the scalp regions overlying the left dorsolateral prefrontal cortex. In contrast, increases in 6.24 Hz EEG power were recorded at sites over the anterior cingulate and right frontal cortex prior to incorrect answers on the mathematical task. Harmony et al. (2001) observed an increase in the power of theta (7.8 Hz) recorded over prefrontal, anterior cingulate, and anterior temporal regions in children while performing a figure categorization task. Harmony et al. (1999) found that the 5.46 Hz frequency was more prominent in the right pre-frontal regions during mental calculation than in control conditions. During a verbal N-back task Krause et al. (2000) found greater 4–6 Hz ERS at anterior electrodes when target stimuli had been presented on previous trials. Caplan and Glaholt (2007) found that, with relational list learning in which presentation of one word from a previously presented list cued recall of a preceding or following word, FM-theta was linked to memory performance and was so more in relation to individual variation across participants than across trials within participants.

FM-theta has also been shown to change dependent on different components of the task. As noted above, Jensen and Tesche (2002) reported the appearance of FM-theta during all facets of the Sternberg task. However, Peterson and Thaut (2002) noted greater 4–8 Hz spectral power at F3 and F4 during 5 and 10 s delay periods compared to 2 s delay periods in a continuous nonverbal auditory working memory task relative to a reference memory task. Furthermore, the context in which tasks are presented during an experiment may be enough to produce changes in FM-theta. Wilson et al. (1999) found that FM-theta increased during the retention period with task difficulty during a working memory experiment, but only in one condition. During condition 1, participants had to remember 1, 3, 5, 7, or 8 items, retain them for 4 s and then recall. For this condition the easiest list length of 1 item was presented on 60% of occasions, and each of the other items made up 40% of the trials. Subsequent testing was conducted where memory sets for each difficulty level were randomly presented (condition 2) or presented in blocks of 40-trials (condition 3) during counterbalanced experiments. No changes in theta were noted at frontal electrodes for the different difficulty levels during this subsequent testing. Theta ERS over anterior, central, and posterior electrode sites during an auditory version of the Sternberg task was shown to be consistent at two different time points spaced approximately 9 days apart (Krause et al., 2001). Relatively high Pearson correlation coefficients between test sessions were noted in the theta frequency range

during both encoding and retrieval compared to other frequency bands. McEvoy et al. (2000) also demonstrated that FM-theta showed reliability during an N-back task both within and between sessions. Sauseng et al. (2004) found that 4–7 Hz theta activity recorded from pre-frontal sites during a two part encoding and retrieval working memory task.

It has also been suggested that the phase of theta may be reset following stimulus presentation in working memory tasks. Research conducted by Luu and co-workers (Luu and Tucker, 2001; Luu et al., 2004) has implicated frontal-midline theta components as being responsible for the error related negativity which is observed during the monitoring of errors. A similar phase reset of hippocampal theta to a simple stimulus occurring in a working memory but apparently not in a reference memory task has been reported in rats (Givens, 1996). However, phase reset can occur (but perhaps to a generally lesser extent) with reference memory (Williams and Givens, 2003) and may be a general mechanism for controlling preferential processing of incoming stimuli (Buzsáki, 2006, Cycle 10).

The majority of the studies have shown an increase in theta power or activity during working memory tasks. However, decreases or absences of change in the activity of theta during task performance could also be useful for unravelling the function of this rhythm. Bastiaansen et al. (2002b) looked at the effects of performing a delayed-response spatial working memory task on theta rhythm. During these trials a circle stimulus was presented to peripheral vision in relation to a centre square fixation point. This circle disappeared after 150 ms during memory trials but remained on sensory trials. The fixation point was removed either 1150 or 4150 ms following trial onset. When the fixation point was removed the participant had to indicate where on the screen the stimulus was presented. What resulted was an increase in induced theta and lower-1 alpha (averaged over 3.9–7.9 Hz) over parietal regions during the display of the stimulus. During retention there was a decrease in induced band power in the theta and lower-1 alpha over frontal electrodes. Furthermore, during the memory trials there was a greater reduction in the theta frequency power recorded over frontal electrodes. Here it was suggested that, depending on the type of function being carried out, certain hippocampo-cortical loops are activated. In this instance, theta in the hippocampo-frontal loop is decreased—in effect reducing noise that may interfere with performance on the task that involves a hippocampo-parietal loop. Similarly slow waves over frontal regions were noted during retrieval of verbal information while spatial information resulted in an increase in slow waves, particularly in parietal regions (Heil et al., 1996, 1997). This is similar to the finding by Pesonen et al. (2007) where ~4–6 Hz activity increased during a visual N-back task particularly over parietal regions. Finally, Raghavachari et al. (2006) found that the gating of theta power, or amplitude enhancement was essentially absent at frontal intracranial cortical sites (see below for details regarding intracranial recordings) for the duration of the trial period during a verbal Sternberg task. However, it was difficult to gauge whether these electrode locations were near frontal-midline sites.

5.3. Spatial navigation tasks

Several studies have looked at theta in relation to virtual spatial navigation tasks. MacKay et al. (2001) examined theta during both a Sternberg verbal working memory task and a virtual maze task. They found that theta tended to be distributed over frontal regions for both tasks, while the working memory task also had left temporal theta activity and the virtual maze task demonstrated concurrent right temporal activity. A number of spatial navigation tasks have involved the use of intracranial EEG (iEEG) in patients with epilepsy.

Kahana et al. (1999), using iEEG in three patients, found increases in theta activity during long versus short mazes, notably over temporal sites. Caplan et al. (2001) examined iEEG in participants with epilepsy while learning a maze. Theta rhythm was the predominant activity that was recorded during the learning of the maze. Furthermore, as the maze length increased the occurrence of theta rhythm also increased. Theta rhythm was widely distributed across the cortex. Caplan et al. (2003) found that theta activity during exploration and goal seeking behaviour in a virtual navigation task had different cortical distributions. In particular widespread theta was noted over motor, temporal, and frontal cortices in Fig. 4 of their data. Fig. 7 of their data revealed greater theta power during the goal seeking task versus the exploration task at a number of sites including the frontal cortex. Ekstrom et al. (2005) found an increase in theta power during virtual navigation at cortical and hippocampal electrode sites. At cortical sites theta recorded from frontal and temporal regions during virtual navigation was greater when searching for randomly distributed targets compared to searching for targets that had fixed locations. Furthermore, the amount of cortical (non-specific) theta recorded correlated with the amount of theta recorded from the hippocampus during segments of navigation. de Araújo et al. (2002) using MEG, found a peak in the 4 Hz range that increased during navigation. Using a single dipole model they localized this source to "near the superior temporal gyrus and the deeper temporal structures (p. 72)." The authors also found that theta activity "propagated" from frontal to posterior regions during the task.

There are a number of advantages and disadvantages to using iEEG (Caplan et al., 2001; O'Keefe and Burgess, 1999). The main advantages are that it is possible to determine with more precision the source of the underlying rhythm at the same time as minimizing muscle and eye-blink artefacts. However, the iEEG recordings are restricted to people in whom there is possible abnormal EEG and abnormal brain function. Thus, there is a sampling bias with greater numbers of electrodes being placed in temporal lobes (Caplan et al., 2001). Furthermore, patients are often taking medications and even if they are not, and recording is from areas with no explicit pathology, the tissue recorded from will potentially have been subjected to abnormal input from patho-logical areas over considerable periods of time. Finally, clinical applications of iEEG only extend to certain population groups and patient numbers are often small.

5.4. Episodic memory tasks

A number of studies have reported the presence of theta ERS activity at frontal electrode sites during the performance of episodic memory tasks. A prominent finding of episodic memory studies is that theta increases during encoding (Klimesch, 1999; Klimesch et al., 1997). Furthermore, theta recorded from frontal and other cortical regions during encoding is related to successful retrieval (Klimesch et al., 1994; Osipova et al., 2006; Sederberg et al., 2003). Similarly, Mölle et al. (2002) reported that effective learning or encoding of pairs of words was related to a synchronization of theta and a desynchronization of alpha over the frontal and temporal regions of the scalp. Klimesch et al. (1994) conducted a study where participants had to later indicate (which participants were not informed about) whether a congruent concept-feature (e.g. eagle-claw) pair had been presented in an earlier semantic task. In the first 375 ms of the pre-stimulus period the power of theta was greatest at frontal electrodes. Following the presentation of a stimulus in the episodic memory task where pairs

had been presented earlier, there was an increase in relative theta power. This tended to decrease at about 375 ms followed by another increase at 750 ms that was most pronounced at frontal electrodes.

There is also an increase in theta following recognition and retrieval. Klimesch et al. (1996a) conducted a study that involved the presentation of 96 words that participants had to initially categorize as living or not living. Without prior warning, later in the experiment participants were required to recall as many of these words as possible. What was found was an increase in the absolute power and event related power (over time) of theta during encoding for words that were later recalled correctly. Furthermore, the power of theta was significantly higher in the left hemisphere and at central and frontal electrode sites. Klimesch et al. (1997) specifically looked at theta synchronization during encoding and retrieval involved in an episodic memory task. For correct trials, both encoding and retrieval components of the task were associated with an increase in the power of theta that was most pronounced over frontal regions. A later study (Klimesch et al., 2001) demonstrated that retrieval compared to encoding was associated with a significantly greater synchronization of theta. This was most pronounced at frontal regions.

Theta synchronization over frontal-midline regions has also been shown to be twice as large following presentation (recognition) of words that had previously been presented (Burgess and Gruzelier, 1997). Similarly, Doppelmayr et al. (1998) investigated ERD and ERS during an episodic recognition memory task that involved having to correctly identify previously presented target stimuli from distractor words. There was greater theta synchronization at all electrode sites in the right hemisphere during retrieval in good performers than bad performers. For the left hemisphere, there was a greater degree of theta synchronization in frontal electrodes compared to central, temporal, parietal, and occipital electrodes.

5.5. Internalised attention and meditation

Several studies have demonstrated that FM-theta increases during periods of sustained internalised attention or meditation (Aftanas and Golocheikine, 2001; Banquet, 1973). Aftanas and Golocheikine (2001) noted an increase in theta (∼4–6 Hz) and alpha 1 (∼6–8 Hz) power over frontal and midline regions in long-term meditators compared to controls and short-term meditators. There was also a synchronization of theta between prefrontal and posterior association cortex with a focal point located in the left prefrontal cortex. Kubota et al. (2001) also conducted a study where participants performed a meditative technique (Su-soko task) that involved focusing on the breath and counting the number of inhalations and exhalations. Performance of this meditative technique produced an increase in the amount of FM-theta (consistent with other meditation studies). Furthermore, the increase in FM-theta correlated with autonomic heart activity including a trend for increased inter-beat interval, increases in cardiac vagal and sympathetic indices. In contrast, cardiac sympathetic activity was inversely related to FM-theta. Asada et al. (1999) also report FM-theta was consistently elicited by recollection of Kanji characters and attention to breathing very slowly in their subjects who were recruited because of their reliable FM-theta. Furthermore, a blissful meditative state attained during internalised attention coincided with an increase in FM-theta power.

5.6. Practical and other tasks that modulate FM-theta

A number of more ecological tasks have been shown to produce FM-theta. Brookings et al. (1996) observed theta rhythm in air traffic controllers while performing simulated air traffic control tasks. High difficulty compared to low difficulty resulted in increased theta recorded from F8, C3, CZ, T4, P3, Pz and P4. During an overload condition there was significantly more theta over frontal regions including Fz. Similarly in a flight simulation task, FM-theta increased as the task was made more difficult (Smith et al., 2001).

Laukka et al. (1995) investigated how FM-theta changes during a driving task. EEG was measured at different stages during each driving trial. At two points in the trial the participant had to choose between different roads on which to travel. The correct road to go down at point 2 was dependent on the road chosen at point 1. Participants had to learn and then practice the different associations between the roads A, B, and C at point 1 and the four road options at point 2. Experimental tests consisting of 180 trials were held the following day. The results demonstrated an increase in the occurrence of FM-theta just prior to the junctions in the road where decisions had to be made. In addition, FM-theta occurred more often on correct trials and while learning, and increased from the first learning trials to the final experimental conditions. The authors noted that this increase reflected 'relaxed concentration after mastering the game'. Similarly, Smith et al. (1999) noted an increase in FM-theta with increased practice during video game playing.

The time spent exploring an object by hand has also been related to the amount of fronto-central theta at the end of the retention period prior to recollection (Grunwald et al., 1999). Furthermore, theta power tended to increase as a function of exploration time. In a similar study it was found that there was a positive correlation between Fz theta power and time of haptic exploration at the beginning of exploration. In contrast, a greater number of electrode sites showed theta that correlated with the end of haptic exploration (Grunwald et al., 2001b).

There is also evidence that different types of thoughts can be differentiated in the EEG. Lehmann et al. (1993) investigated the correlation between self-reported thoughts and EEG activity. When a tone occurred participants had to describe what went through their mind previously. All participants were administered diazepam, pyritinol/encephabol, or placebo in a pseudo-random order on different days. The reports were coded into either a visual imagery or abstract thought category (planning/organization). Abstract thoughts were associated with more anterior source localization of EEG notably in the delta/theta (defined as 1–7.5 Hz) range. The administration of diazepam increased the difference in anterior–posterior localization of delta/theta between abstract thoughts and visual imagery.

Nishikori et al. (1985) noted that the photopalpebral reflex latency was shortened while the auditory evoked response latency was lengthened during performance of an arithmetic task in participants who reliably demonstrated FM-theta. Dietl et al. (1999) applied electrical stimuli in trains that lasted for 30 s to the index finger of participants. What resulted was a transient increase in FM-theta that quickly habituated and returned to baseline.

Martin (1998) found that in right frontal electrodes there was a decrease in the frequency of theta when participants were presented with the odour spearmint compared to no odour or the odour chocolate compared to almond and cumin. A further experiment revealed a significant decrease in theta recorded from Fz when participants were presented with chocolate compared to other smells.

6. Personality factors, drugs and neurochemistry

There is a sense in which variations in personality can be thought of as equivalent to variations in the level of chronic

administration of a drug. Thus, a person with a low level of neuroticism could be thought of as equivalent to a person receiving chronic administration of an anti-anxiety drug. We will consider personality and drugs together, therefore, in this section.

6.1. Personality and theta

The earlier work of Mizuki et al. (1984, 1976) revealed that FM-theta was more likely among certain personality types. In particular, Mizuki et al. (1984, 1976) reported that FM-theta was more likely in extrovert, less neurotic, and less anxious subjects. Yamaguchi et al. (1981) looked at FM-theta in 12 students and also noted low neurotic scores in subjects who displayed FM-theta. Consistent with the known linkage of neuroticism with anxiety disorders, Suetsugi et al. (2000) reported that the appearance of FM-theta might be related to the relief of anxiety in patients with generalised anxiety disorder. Knyazev and Slobodskoj-Plusnin (2007) found that high drive (a dimension of behavioural activation) was associated with greater theta and gamma activity at frontal electrode sites during reward compared to punishment situations. Similarly, Aftanas et al. (2003) has also found differences in theta band activity asymmetries at frontal cortical sites between high and low anxious individuals dependent on whether the information presented was threatening or pleasant. However, although anxiety and personality traits such as behavioural inhibition have also been linked to activity in other frequency bands including delta, alpha, and gamma (Knyazev, 2007; Knyazev et al., 2004, 2005, 2006; Robinson, 2001) and to other brain regions including hemispheric differences in spectral power (Aftanas and Pavlov, 2005; Coan and Allen, 2004; Davidson, 2004); these areas of research are beyond the scope of the present review.

6.2. Drug interactions with hippocampal theta

Before considering the reported effects of drugs on FM-theta it is useful to consider the extensive literature on the effects of drugs on hippocampal theta for two reasons. First, the effects of such drugs as can be compared between frontal and hippocampal theta appear to be opposite with, for example, anxiolytic drugs (for definition see Section 6.3.1) decreasing hippocampal theta and increasing FM-theta. Second, there are marked differences in the ways that different classes of drug affect hippocampal theta (changing "gating", amplitude, or frequency); and these different types of action will usually be conflated as simple changes in power with the methods normally used to assess FM-theta. The effects of drugs on hippocampal theta have recently been reviewed by McNaughton et al. (2007). They link different aspects of change in theta to anxiolytic and procognitve actions, respectively:

"Hippocampal damage produces cognitive deficits similar to dementia and changes in emotional and motivated reactions similar to anxiolytic drugs. The gross electrical activity of the hippocampus contains a marked 'theta rhythm'. This is a relatively high voltage sinusoidal waveform, resulting from synchronous phasic firing of cells, variation in which correlates with behavioural state. Like the hippocampus, theta has been linked to both cognitive and emotional functions. Critically, it has recently been shown that restoration of theta-like rhythmicity can restore lost cognitive function. We review the effects of systemic administration of drugs on hippocampal theta elicited by stimulation of the reticular formation. We conclude that reductions in the frequency of reticular elicited theta provide what is currently the best in-vivo means of detecting antianxiety drugs. We also suggest that increases in

the power of reticular-elicited theta could detect drugs useful in the treatment of disorders, such as dementia, that involve memory loss. We argue that these functionally distinct effects should be seen as indirect and that each results from a change in a single form of cognitive–emotional processing that particularly involves the hippocampus." (McNaughton et al. (2007) p. 329)

With the administration of anxiolytic agents (including ethanol, for pharmacology see Section 6.3.2) and anaesthetic agents such as urethane there is a decrease in the frequency of hippocampal theta rhythm elicited by stimulation of the reticular formation. The administration of ethanol has also been demonstrated to decrease the frequency of spontaneous theta while at the same time disrupting working memory related to spatial navigation on a T-maze (Givens, 1995).

In contrast, the administration of cholinergic antagonists including atropine and scopolamine does not change the frequency of theta rhythm but instead completely prevents its occurrence under some behavioural conditions but not others. These drugs are much more amnesic and less anxiolytic than the classical anxiolytic drugs. Consistent with this, there are preliminary data that a range of "pro-cognitive" drugs increase the power, but not necessarily the frequency, of theta.

6.3. Drug interactions with FM-theta

As noted above, there is a relationship between FM-theta and personality traits. Furthermore, transcranial magnetic stimulation has been shown to reduce anxiety while at the same time increasing theta in the left prefrontal region (Schutter et al., 2001). This has lead to a number of studies into drug interactions with FM-theta (Table 3). These studies typically concentrate on the spectral power of FM-theta, in subjects grouped based on the initial presence of FM-theta in their EEG, while completing the Uchida-Kraepelin task (Kuraishi et al., 1957) before and after the administration of a drug.

6.3.1. Anxiolytic drugs

Anxiolytic (anti-anxiety) drugs are compounds used to treat anxiety disorders, and particularly generalised anxiety, in the clinic. More modern anxiolytics are also panicolytic and anti-depressant (e.g. fluoxetine/Prozac), however, anxiolytic action does not entail these other effects. Many of the older anxiolytics (barbiturates, meprobamate, benzodiazepines) bind to a variety of sites on the GABA-A receptor in the brain, increasing the action of, and in some cases mimicking the action of, the inhibitory neurotransmitter GABA (Haefely, 1990a,b; Teicher, 1988). Other drugs, that are anxiolytic but not sedative or anaesthetic, bind to the 5-HT$_{1A}$ receptor (Goldberg, 1984; Goldberg and Finnerty, 1979).

Mizuki et al. (1989, 1982) reported that diazepam (a benzodiazepine), amobarbital (a barbiturate), placebo, and methylphenidate (Ritalin, a stimulant that releases monoamines) all increased the amount of FM-theta in participants who initially did not show FM-theta. Furthermore, scores on Spielberger's State Trait Anxiety Inventory (STAI) decreased following the administration of these drugs. In a subsequent study where participants were selected based on initial appearance of FM-theta, diazepam resulted in an increase in FM-theta and a decrease in STAI scores, but did not impact performance of the Uchida-Kraepelin task (Mizuki et al., 1986, 1981). Amobarbital had no effect on FM-theta or STAI scores and decreased performance. Administration of methylphenidate resulted in an increase in STAI scores and improved performance. Placebo increased FM-theta, reduced STAI

Table 3
Drug interactions with FM-theta

Drug class	Drug	Subjects	Effects on amount of FM-theta	Effects on task performance	Effects on STAI scores	Investigators
Adrenergic alpha-agonists	Clonidine	FM-group	dec	dec	No change	Mizuki et al. (1996)
Adrenergic alpha-agonists	Clonidine	Non-FM-group	inc	No change	dec	Mizuki et al. (1996)
Adrenergic alpha-antagonists	Yohimbine	FM-group	No change	inc	No change	Mizuki et al. (1996)
Adrenergic alpha-antagonists	Yohimbine	Non-FM-group	dec	inc	inc	Mizuki et al. (1996)
Antiepileptic	Phenytoin	–	No change	No change	–	Chung et al. (2002)
Antihistamine	Diphenhydramine	–	dec (high wm load)	dec	–	Gevins et al. (2002)
Azaspirodecanediones (anxiolytic)	Buspirone	FM-group	inc	inc	dec	Mizuki et al. (1994)
Azaspirodecanediones (anxiolytic)	Buspirone	Non-FM-group	No change	No change	No change	Mizuki et al. (1994)
Barbiturate	Amobarbital	FM-group	No change	dec	No change	Mizuki et al. (1981)
Barbiturate	Amobarbital	Non-FM-group	inc	–	dec	Mizuki et al. (1982)
Barbiturate	Amobarbital	FM-group	No change	dec	No change	Mizuki et al. (1986)
Barbiturate	Amobarbital	Non-FM-group	inc	dec	dec	Mizuki et al. (1989)
Benzodiazepine	Diazepam	FM-group	inc	No change	dec	Mizuki et al. (1981)
Benzodiazepine	Diazepam	Non-FM-group	inc	–	dec	Mizuki et al. (1982)
Benzodiazepine	Diazepam	Non-FM-group	inc 6/16[a]	dec	dec	Inanaga et al. (1983)
Benzodiazepine	Diazepam	Non-FM-group	inc 6/16[a]	dec	dec	Mizuki et al. (1983)
Benzodiazepine	Diazepam	FM-group	inc	No change	dec	Mizuki et al. (1986)
Benzodiazepine	Diazepam	Non-FM-group	inc	dec	dec	Mizuki et al. (1989)
Benzodiazepine profile	Zoplicone	Non-FM-group	inc 5/16[a]	dec	–	Inanaga et al. (1983)
Benzodiazepine profile	Zoplicone	Non-FM-group	inc 5/16[a]	dec	dec	Mizuki et al. (1983)
CNS depressant	Ethanol	–	inc	–	–	Mukasa (1980)
CNS depressant	Ethanol	–	inc	–	–	Ehlers et al. (1989)
CNS depressant	Ethanol	–	inc	dec	–	Laukka et al. (1997)
CNS depressant	Ethanol 0.08 (BAC)	–	inc	dec	–	Gevins and Smith (1999)
CNS depressant	Ethanol 0.02 (BAC)	–	inc	dec	–	Gevins and Smith (1999)
CNS depressant	Ethanol	–	inc	dec	–	Ilan and Gevins (2001)
CNS depressant	Ethanol	–	inc	No change	–	Gevins et al. (2002)
CNS depressant	Ethanol	–	inc	–	–	Tran et al. (2004)
CNS stimulant	Methylphenidate	FM-group	No change	inc	inc	Mizuki et al. (1981)
CNS stimulant	Methylphenidate	Non-FM-group	inc	–	dec	Mizuki et al. (1982)
CNS stimulant	Methylphenidate	FM-group	No change	inc	inc	Mizuki et al. (1986)
CNS stimulant	Methylphenidate	Non-FM-group	inc	inc	dec	Mizuki et al. (1989)
CNS stimulant	Caffeine (exclude)	–	–	No change	–	Gevins et al. (2002)
Dopamine agonists	Bromocriptine	FM-group	No change	No change	No change	Mizuki et al. (1997)
Dopamine agonists	Bromocriptine	Non-FM-group	inc	No change	dec	Mizuki et al. (1997)
Dopamine antagonist	Sulpiride	FM-group?	No change	–	–	Nakamura and Mukasa (1990)
Dopamine antagonist	Haloperidol	–	inc	–	–	Westphal et al. (1990)
Dopamine blocker	Sulpiride	FM-group	inc	No change	dec	Mizuki et al. (1997)
Dopamine blocker	Sulpiride	Non-FM-group	dec	No change	inc	Mizuki et al. (1997)
Dopamine precursor	L-DOPA (600 mg)	FM-group?	inc	–	–	Nakamura and Mukasa (1990)
Dopamine releaser	DN-1417	FM-group?	inc	–	–	Nakamura and Mukasa (1990)
MAO inhibitor	Safrazine	FM-group?	No change	–	–	Nakamura and Mukasa (1990)
NA and serotonin uptake inhibitor	Clomipramine	FM-group	No change	No change	No change	Suetsugi et al. (1998)
NA and serotonin uptake inhibitor	Clomipramine	Non-FM-group	inc	No change	dec	Suetsugi et al. (1998)
Noradrenaline precursor	L-threo-DOPS	FM-group?	No change	–	–	Nakamura and Mukasa (1990)
Placebo	–	FM-group	inc	inc	dec	Mizuki et al. (1981)
Placebo	–	Non-FM-group	inc	–	dec	Mizuki et al. (1982)
Placebo	–	Non-FM-group	inc 6/16[a]	No change	No change	Inanaga et al. (1983)
Placebo	–	Non-FM-group	inc 6/16[a]	inc	No change	Mizuki et al. (1983)
Placebo	–	FM-group	inc	inc	dec	Mizuki et al. (1986)
Placebo	–	Non-FM-group	inc	inc	dec	Mizuki et al. (1989)
Placebo	–	FM-group?	No change	–	–	Nakamura and Mukasa (1990)
Placebo	–	Mixed	inc	inc	–	Nakamura and Mukasa (1992)
Placebo	–	FM-group	No change	inc	No change	Mizuki et al. (1994)
Placebo	–	Non-FM-group	No change	inc	No change	Mizuki et al. (1994)
Placebo	–	–	inc	No change	–	Chung et al. (2002)
Thienodiazepine anxiolytic	Etizolam	Mixed	No change	inc	–	Nakamura and Mukasa (1992)
Yhienodiazepine anxiolytic	Clotiazepam	Mixed	inc	inc	–	Nakamura and Mukasa (1992)

'FM-group' indicates subjects specifically selected because they reliably express FM-theta. 'non-FM-group' indicates subjects specifically selected because they reliably do not express FM-theta. '–' indicates that no data was supplied. wm indicates working memory.
[a] '5/16' implies that 5 subjects out of 16 showed the reported change.

scores and improved performance. Overall, diazepam caused the greatest increase in the appearance time of FM-theta compared to the other drugs.

Table 3 further reveals that zopiclone (a novel drug with a pharmacological profile like a benzodiazepine), like diazepam, increases the amount of FM-theta (Inanaga et al., 1983; Mizuki et al., 1983). FM-theta tended to persist longer on average after the administration of diazepam compared to zopiclone. It was also reported that placebo increased the amount of FM-theta in some non-FM as well as FM subjects. The general trend is that

anxiolytics such as the barbiturates and benzodiazepines increase FM-theta.

The anxiolytic medications described so far act on the GABA-A receptor and have quite distinct side effects from novel anxiolytics that act at other receptors including 5-HT and NA. It is an important point that, as with effects on hippocampal theta, novel anxiolytics have been shown to produce similar changes in FM-theta to classical ones—these effects being, in both cases, opposite to the effects of the same drugs on hippocampal theta.

Mizuki et al. (1994) examined the effects of buspirone (a 5-HT$_{1A}$ partial agonist) on FM-theta and State Trait Anxiety levels while completing the Uchida-Kraepelin test. Participants were broken into groups based on whether FM-theta was initially present or not in EEG records. Increases in the occurrence of FM-theta were noted in the FM-theta group after the administration of buspirone with a greater increase noted for 15 mg compared to 5 mg doses. The occurrence of FM-theta did not increase in the non-FM-theta group. State anxiety scores decreased significantly more in the FM-theta group compared to the non-FM-theta group while there was an increase in performance on the Uchida-Kraepelin task in the FM-theta group. This increase in performance is in contrast to the decrease or no change in performance noted after the administration of diazepam. The administration of clomipramine (a tricyclic drug that inhibits uptake of both 5HT and noradrenaline and would, among other actions, be likely to increase agonist action at 5-HT$_{1A}$ receptors) has been shown to increase the amount of FM-theta and decrease STAI scores in individuals who did not initially demonstrate FM-theta (Suetsugi et al., 1998). In contrast, higher doses (30 mg) of clomipramine had no effect on STAI scores while increasing FM-theta. In participants who initially demonstrated FM-theta no changes in STAI or FM-theta amounts were noted after the administration of clomipramine.

Nakamura and Mukasa (1992) reported that the thienodiazepine anxiolytics clotiazepam but not etizolam increased the appearance of FM-theta, particularly in participants with high neuroticism and anxiety scores. However, this study did not show a relationship between state and trait anxiety and FM-theta. It is possible that a low baseline level of anxiety could have restricted the extent of this relationship. It was suggested that etizolam did not increase FM-theta because of the greater degree of drowsiness caused by this drug which is used as a sedative. However, it should be noted that Strijkstra et al. (2003) found that sleepiness increased the amount of theta recorded at frontal electrodes.

From these studies it can generally be concluded that the administration of anxiolytic drugs produces an increase in FM-theta and a decrease in STAI scores. Furthermore, it is suggested that FM-theta could be an effective tool for gauging anti-anxiety drug action and anxiety relief in clinical populations. There is also some indication that the initial presence or absence of FM-theta may mediate drug effects. In parallel with this, personality variables can possibly mediate the effects of anxiolytic medications on FM-theta.

6.3.2. Alcohol and FM-theta

Alcohol is primarily of interest because of its use as a recreational drug that can, for example, impair driving. However, an important feature of its pharmacology is a similar action on the GABA-A receptor to anxiolytic drugs such as benzodiazepines and barbiturates and, as a result, it has similar effects to all other classes of anxiolytic drug on hippocampal theta rhythm (Coop et al., 1990; McNaughton et al., 2007).

Perhaps the most consistent result in EEG studies with ethanol in humans is an increase in alpha activity (Ilan and Gevins, 2001; Little, 1999). However, a number of studies have shown changes in the theta range at frontal electrode sites. Mukasa (1980) reported

that the ingestion of a small amount of alcohol increased the appearance time of FM-theta during performance on the Uchida-Kraepelin task. Ehlers et al. (1989) found that after the administration of 0.75 ml/kg of 95% ethanol that there was an increase in the power of theta (4–7 Hz) activity recorded by an anterior electrode. Furthermore, it was noted that there was a reduction in the peak frequency within the theta range that contained the greatest amount of power at a frontal electrode. Similarly, Krause et al. (2002) found that alcohol reduced event related synchronization in the 6–8 Hz range during encoding at anterior and central electrode locations. These two results are consistent with Givens (1995) study whereby high doses of ethanol (0.75–1.0 g/kg) started to produce a decrease in the peak frequency and power of hippocampal theta in rats.

Laukka et al. (1997) also examined the effect of alcohol on FM-theta, but on this occasion during the performance of a driving task that involved performing two turns in relation to traffic signs during each trial. Increases in FM-theta were noted after the appearance of a traffic sign and with the correct road selection. Furthermore, alcohol consumption produced a significant increase in FM-theta compared to control conditions. Ilan and Gevins (2001) examined the influence of wine consumption over an extended duration on the EEG and found that 4–6 Hz activity increased at Fz. Gevins et al. (2002) reported that the administration of alcohol produced an increase in spectral power of theta during rest conditions and during performance of the N-back memory task. During performance of the N-back task this increase was found to occur over frontal-midline regions. Gevins and Smith (1999) looked at how both acute intoxication and fatigue/hangover affected EEG during the spatial version of the N-back task. During the acute stage there was a trend for reduced accuracy and increased FM-theta. During the fatigue/hangover stage accuracy was impaired and FM-theta was enhanced. However, it was suggested that this may have resulted from overlap with a diffuse theta signal. Further analyses revealed FM-theta to be sensitive to working memory load but not to breath alcohol level. The authors suggested that there is a separate "fatigue sensitive diffuse theta rhythm" that is different to the FM-theta that changes with working memory load.

6.3.3. Adrenergic and dopaminergic drugs

Research by Mizuki et al. (1996) looked at clonidine and yohimbine (agonist and antagonist, respectively, at the alpha 2 receptor (which is a noradrenaline receptor involved in the control of blood vessels and related changes in arousal—clonidine is sometimes prescribed for anxiety) and their impact on STAI scores and FM-theta. The adrenergic agonist clonidine increased the amount of FM-theta and reduced STAI scores in the non-FM-group, while it decreased FM-theta in the FM-group. The adrenergic antagonist yohimbine decreased FM-theta, increased STAI scores, and increased errors on the Uchida-Kraepelin task in the non-FM-theta group but had little effect in the FM-theta group.

Mizuki et al. (1997) have also investigated the effect of bromocriptine (a dopamine agonist) and sulpiride (a dopamine D2 receptor antagonist) on STAI scores and FM-theta in an FM-theta group compared to a non-FM-theta group. Bromocriptine increased the amount of FM-theta and reduced STAI scores in the non-FM-theta group whereas it had no effect in participants in the FM-theta group. Sulpiride increased FM-theta and reduced STAI scores in the FM-theta group but had the opposite effects in the non-FM-theta group.

6.3.4. Other psychotropics and FM-theta

The neuroleptic haloperidol (which acts at the dopamine D2 receptor) has been shown to increase the power of theta in frontal,

central, and parietal regions (Westphal et al., 1990). Chung et al. (2002) looked at the effects of 10 mg of phenytoin (an anticonvulsant) on EEG in participants performing the spatial component of the continuous N-back task. When the difficulty of the task was increased (2-back condition) there was an increase in the power of FM-theta. However, with the administration of phenytoin no increase in FM-theta was observed. Finally, administration of diphenhydramine (an antihistamine with sedative effects) produced a decrease in FM-theta during high work load on the N-back task. Essentially this reversed the typical FM-theta increase with load effect (Gevins et al., 2002).

6.4. Neurochemistry

Several studies have identified correlations between the amounts of FM-theta observed in particular individuals and neurochemical measures. Importantly, the variations in FM-theta have typically been predictive of variation in response to the subsequent administration of a drug. This suggests that the correlates are likely to have direct causal significance.

The main correlation that has been focused on is a negative correlation between production of FM-theta and platelet monoamine oxidase (MAO). This was linked to personality in that subjects with high scores on extraversion had high FM-theta and low MAO (Hashimoto et al., 1988; Nakamura and Mukasa, 1990). Gallinat et al. (2006) recently found a positive relationship between the appearance of FM-theta recorded post-stimulus in an auditory oddball task and hippocampal glutamate concentrations determined using MRI. Possibly consistent with this, frontal-theta activity levels are negatively related to hippocampal volumes in participants with mild cognitive impairment and mild dementia (Grunwald et al., 2001a).

Administration of buspirone (a $5HT_{1A}$ receptor partial agonist) caused a decrease in 5HT and 5-HIAA levels, state anxiety score, and an increase in FM-theta in the FM-theta group (Mizuki et al., 1994). In contrast, the only effect in the non-FM-theta group following buspirone administration was a slight increase in 5HT. The opposite effects of buspirone on 5HT and on anxiety in the FM-theta group, here, are not as paradoxical as they might seem. Increases in 5HT (as with specific serotonin reuptake inhibitors) would normally be associated with decreased anxiety. But this is likely to be through an action on postsynaptic $5HT_{1A}$ receptors. Buspirone acts on $5HT_{1A}$ autoreceptors to reduce 5HT levels—but at the same time binds to the postsynaptic $5HT_{1A}$ receptors that would otherwise be occupied by serotonin and so produces its anxiolytic action.

Clonidine is an alpha receptor agonist which is sometimes prescribed for the relief of anxiety. It produces a decrease in 3-methoxy-4-hydrophenylglycol, a metabolite of noradrenaline, while at the same time reducing levels of FM-theta in the FM-theta group (Mizuki et al., 1996). The change in FM-theta in relation to the implied change in anxiety is, here, the opposite of that seen with buspirone.

Bromocriptine, a dopamine agonist, produced a decrease while sulpiride caused an increase in the level of the catecholamine metabolite homo-vanillic acid (HVA) (Mizuki et al., 1997). The bromocriptine produced no change in FM-theta in the FM-theta group while increasing it in the non-FM-theta group. In contrast, sulpiride, a dopamine D2 receptor antagonist increased FM-theta in the FM-theta group and decreased FM-theta in the non-FM-theta group.

The administration of clomipramine, a tricyclic antidepressant that increases levels of both serotonin and noradrenaline has been shown to reduce levels of the serotonin metabolite 5-HIAA in a non-FM-theta group while at the same time increasing FM-theta (Suetsugi et al., 1998).

These data are too fragmentary to allow detailed conclusions to be drawn. However, they link variation in FM-theta very strongly to variation in monoamine (dopamine, noradrenaline and serotonin) systems and suggest that not only the levels of these monoamines but also the relatively balance between them may be important in the control of FM-theta. A final neurochemically related result, is that Nishijima et al. (1985) reported that administration of DN-1417 (a thyroid releasing hormone analog) increased appearance time of FM-theta.

6.5. Personality, drugs and neurochemistry—conclusions

While a range of specific compounds have been tested in relation to FM-theta, most are anxiolytic drugs. The main conclusion to be drawn is that such drugs increase FM-theta and this effect is apparently nearly as reliable as the decrease in hippocampal theta produced by anxiolytic drugs of all chemical classes. The fact that novel and classical anxiolytics have similar effects indicates a link with processes involved in or that can give rise to clinical anxiety and rules out a relation with side effects such as muscle relaxation, anticonvulsant action and addiction that are not shared between novel and classical anxiolytics. Consistent with this, the same drugs often reduce state anxiety. Effects on task parameters are more mixed but this is difficult to interpret as the main tasks used are not designed to test anxiety and mixed effects could be the result of non-linear interactions of task performance with arousal.

Consistent with the apparent relation of state anxiety (or some related psychological process) to FM-theta shown by the drugs is the linkage with the personality factor of neuroticism. This is a predisposing risk factor for the anxiety disorders treated by anxiolytic drugs (as well as for a range of related phobic disorders that are not sensitive to anxiolytics).

While linkages with monoamines have been discovered and these systems are changed by the novel anxiolytic drugs, there is no clear picture as to the direction of the linkages. The reported correlation with MAO is consistent with the reported drug effects on FM-theta, while the monoamine levels themselves show an opposite effect.

7. Coherence studies

The processing of complex information is likely to involve interaction between multiple regions of the brain. Rhythmic activity in one area is likely to be communicated to another and so generate a temporal linkage in the rhythmicities in the two structures. Over and above this, it has been suggested that such synchronous rhythmicity may be important for the correct processing of information—and it has recently been shown that, at least in the hippocampus, rhythmicity, in and of itself, has a functional role.

Assessment of coherence (i.e. phase correlation extracted from the Fourier transform) determines the degree of synchrony between activity recorded at different electrodes. A number of studies have used this to assess how frontally recorded theta relates to theta recorded at other sites.

Some critical limitations should be taken into account when considering the results of such analysis. First, coherence between a pair of electrodes can increase not only because there are two distinct sources, activity in which has become more phase-locked, but also because a single source generates a signal that reaches both electrodes. Second, increased coherence in the theta range over a brief time period can occur as the result of evoked potentials (and/or phase reset) that are not the result of a functional interaction between the two sources that are being assessed for coherence.

Table 4
Results from papers demonstrating phase-locking and coherence at frontal and/or hippocampal theta

Investigators	FMTFC	Task	Methodology	Details
Aftanas and Golocheikine (2001)	3.77–5.66 Hz	Meditation	Coherence	Long-term meditators elicited coherence between left prefrontal (AF3) and posterior cortex.
Cantero et al. (2003)	4–7 Hz	Sleep stages and wakefulness	Coherence (iEEG)	Absence of coherence between hippocampal and cortical electrodes sites
Cohen et al. (2007)	4–8 Hz	Probabilistic reinforcement learning task	Wavelet analysis, phase-analysis of trials at Fz	Decreasing reward probability increased theta phase coherence following wins but not losses. Theta phase coherence was greater following losses compared to wins.
Fell et al. (2003)	4–7 Hz	Verbal declarative memory task	Wavelet analysis, phase-analysis, Coherence (iEEG)	Increased theta coherence between hippocampus and rhinal cortex. This was also related to gamma phase synchronization between the same sites
Luu and Tucker (2001)	4–7 Hz	Speeded response task	Phase-locking	Phase-locking of frontal-midline theta contributes to the error related negativity (ERN)
Luu et al. (2004)	4–7 Hz	Speeded response task	Phase-locking	Phase-locking of frontal-midline theta contributes to the error related negativity (ERN)
Makeig et al. (2002)	6 Hz	Visual Selective Attention	Non-random phase distribution, averaging, inter-trial coherence, independent component analysis	6 Hz theta accounted for variance of N1 at fronto-central sites
Moore et al. (2005)	4–6 Hz	Continuous Go/No-Go task	Coherence	Increased global coherence including frontal electrodes
Mormann et al. (2005)	4–8 Hz	Continuous word recognition task	Wavelet analysis, phase-locking (iEEG)	Phase reset in temporal and hippocampal regions following stimulus presentation
Rizzuto et al. (2003)	7–16 Hz	Sternberg memory task	Wavelet analysis, phase-locking (iEEG)	Phase-reset with stimulus presentation in cortical and hippocampal brain regions
Rizzuto et al. (2006)	6–13 Hz	Sternberg memory task	Wavelet analysis, phase-locking (iEEG)	Phase-reset with stimulus presentation in temporal brain regions
Sarnthein et al. (1998)	4–7 Hz	Sternberg memory task verbal and visual-spatial task	Coherence	Increase in coherence between prefrontal and posterior association cortex during retention period
Sauseng et al. (2002)	IAF theta	Long-term memory and working memory task	Phase direction	Theta spreads between frontal and posterior electrode sites during retrieval from long-term memory
Sauseng et al. (2004)	4–7 Hz	Visual-spatial-labelling encoding and retrieval	Coherence	Encoding = frontal–T6 coherence; retrieval = frontal to bilateral T5 and T6
Sauseng et al. (2005)	3.9–6.8 Hz	Visual-spatial working memory task	Coherence	Increased theta coherence between frontal and parietal sites in difficult visual-spatial comparison condition versus retrieval condition
Sauseng et al. (2006)	4–7 Hz	Working memory switch or stay paradigm	Coherence	Increased frontal to posterior coherence during a switch compared to stay trial
Sauseng et al. (2007)	4–7 Hz	Complex sequential finger movements	Coherence	Increased coherence in frontal and parietal regions during performance of novel finger movement sequences
Schack et al. (2002)	4–7 Hz	Sternberg task	Bispectral analysis	Memorization of numbers increased phase-coupling between theta recorded from Fz with gamma at Fp1
Summerfield and Mangels (2005)	4–8 Hz	Item-context word recognition task	Wavelet analysis, independent component analysis, coherence	Item only retrieval = increased left fronto-posterior coherence during encoding; item + context retrieval = late bilateral coherence during encoding
Tesche and Karhu (2000)	4–8 Hz	Sternberg task	Phase-locking (MEG)	Phase reset of theta in the right hippocampus in anticipation of and in the left hippocampus following probe presentation
Von Stein and Sarnthein (2000)	4–8 Hz	Working memory	Coherence	Increased fronto-parietal coherence during the retention period
Weiss et al. (2000)	5–7 Hz	Encoding of nouns	Coherence	Increased coherence across the scalp during encoding of words that were correctly recalled

7.1. Human studies: coherence between surface EEG and deep brain regions

Despite a number of studies that have examined the relationship between EEG recorded at different electrodes on the scalp relatively few studies have looked at the coherence between activity recorded at intracranial sites and scalp sites in humans. Brazier (1968) found that adjacent electrodes recording activity within the hippocampus could have different correlations with scalp recorded EEG. Furthermore, activity within the posterior hippocampus was often independent of activity at anterior sites. A strong coherence was noted between posterior hippocampus and the EEG at T4–T6 at 8 and 12 Hz. Another study

showed that the coherence between theta recorded at rhinal cortex and hippocampus correlated with the coherence of gamma at these sites (Fell et al., 2003). Asada et al. (1999) found that when 6–7 Hz activity was recorded from frontal EEG channels, MEG sensors found 6–7 Hz activity in both frontal and temporal regions.

7.2. Human studies: coherence between FM-theta and other brain regions

A number of studies have used coherence analysis to assess how frontally recorded theta relates to theta recorded at other sites during a variety of memory tasks. Components of tasks or cognitive

functions such as working memory can also be disentangled using assessment of connectivity as an additional tool to simple power spectral analysis. Table 4 provides details regarding experiments that have examined coherence between different brain regions and/or phase-locking.

Coherence in the theta band during encoding has been found during a simple memory task for concrete and abstract nouns (Weiss et al., 2000). Here coherence averages were significantly higher when words were correctly recalled. It was also found that there was greater coherence between adjacent electrodes versus more separated electrodes. For concrete nouns there was increased coherence for adjacent electrodes whereas for abstract nouns there was greater coherence between separated electrodes. Correctly recalled nouns demonstrated left hemispheric coherence between frontal and temporo-occipital sites. Concrete nouns also showed an increased coherence between frontal electrode sites and temporal sites in the right hemisphere for correct versus incorrect recall. Coherence between hemispheres is mainly situated in anterior frontal and temporal sites for concrete nouns. Abstract nouns that were correctly recalled showed increased interhemispheric coherence between right frontal EEG and left posterior sites. An increase in coupling in the theta frequency band between frontal EEG recorded at F7, F3, F4, F8 with theta recorded at T6 was noted during encoding of visual patterns presented after acoustically presented number labels (Sauseng et al., 2004). During retrieval there was greater coupling between F7 and F3 with both T5 and T6 and F4 with T6. Theta power also tended to be greater at frontal sites and during the process of retrieval. In comparison, encoding was associated with coupling of frontal regions to right temporal regions whereas the process of encoding was associated with coupling to bilateral temporal regions. It has also been noted that theta spreads between frontal and posterior regions during performance of a memory task (Sauseng et al., 2002). For example, a change in phase direction occurred after about 800 ms in a task that involved recollection of information from long-term memory. Coinciding with phase direction changes were changes in the frequency of EEG. During retrieval there tends to be a shift in theta from anterior to posterior sites, once information is retrieved theta shifts from the posterior sites back to the anterior sites.

Sauseng et al. (2005) conducted a study whereby participants were initially trained to associate eight patterned visual objects consisting of black bars with verbal titles. In the actual test condition participants were presented with two serially presented verbal titles. Participants had to initially imagine (retrieval condition) each of the corresponding objects before making a mental comparison between the two objects according to a criterion such as length (executive condition). An increase in theta coupling was noted between distant frontal and parietal networks during the more difficult executive condition. Sauseng et al. (2007) also found an increase in coherence between frontal and parietal sites during performance of novel finger sequences. It was suggested that this reflected an "integration of sensory information into executive control components of complex motor behaviour (p. 587)" or "reflects the central executive integrating different memory and information processing functions."

Evidence of coherence has also been shown during tasks that involve some form of conflict or necessitate a change in response. Moore et al. (2005) found a general increase in theta coherence across the scalp during goal conflict situations in a go/no-go task. Sauseng et al. (2006) used a switching task where participants had to indicate whether each number presented was greater or less than 5 (when numbers were red) or odd or even (when numbers were green). The colour of the numbers remained the same for up to three trials before switching to the other colour. Greater 4–7 Hz coherence was observed between pre-frontal with occipital and

prefrontal with temporo-parietal electrodes during the switch condition compared to the same condition. Similarly, enhanced theta recorded at Fz has also been noted during a task that involves accumulative summation or a switching response to the presentation of even and odd numbers (Wei et al., 1998).

As noted earlier, FM-theta occurs strongly in working memory tasks. Depending on the type of task different regions of the brain can be co-activated. Sarnthein et al. (1998) found increased 4–7 Hz coherence between frontal and posterior association cortex during retention periods involved in a verbal and a visuo-spatial working memory task. During the verbal task, coherence was stronger between frontal and left posterior regions compared to right posterior regions. During the visuo-spatial task coherence with the left posterior region was similar to that noted on the verbal task, while there was greater coherence with right posterior regions. Less coherence was observed during perception intervals when stimuli were presented to the participant.

Schack et al. (2002) had participants perform a modified Sternberg Paradigm which used either written words or rectangular figures for the stimuli lists and probes. Theta power was maximal at Fz and Cz during retention periods. Furthermore, coherence and strong phase coupling was noted between theta frequencies recorded at Fz and 20–30 Hz frequencies recorded at Fp1.

Recently, Sederberg et al. (2003) looked at intracranial cortical and subcortical theta and gamma oscillations in epileptic patients during the encoding stage in a basic memory task. The task involved the presentation of lists of 20 nouns, followed by an arithmetic distraction task before the recollection of nouns in the memory list. A relationship was observed between increased theta activity in right frontal and temporal regions during encoding and later correct recall—although coherence itself was not assessed.

7.3. Animal studies: theta coherence between hippocampus and other brain regions

As noted above several studies have linked hippocampal theta to theta recorded in frontal cortex in humans. There are similar findings in rats. Siapas et al. (2005) found that prefrontal theta activity was phase-locked to hippocampal theta activity. Similarly, Jones and Wilson (2005) found that theta activity in medial prefrontal cortex preceded activity recorded from CA1 in the hippocampus. In a preliminary mapping study of midline cortex, Young and McNaughton (2008) found low frequency theta activity in frontal sites during stillness and grooming behaviour that was not matched by posterior cortex or hippocampal rhythmicity; whereas, with movement and particularly exploratory rearing, frontal sites showed higher frequency power that was coherent with hippocampal theta activity. Thus, frontal cortex showed different theta-range rhythmicities at different times that could be independent of, or coherent with, hippocampus.

8. Discussion

The purpose of this review was to summarise the research and literature to date on FM-theta and to interpret the findings, where appropriate, with what is known of theta recorded from the hippocampus. FM-theta was chosen as a starting point because, by and large, it has been the most commonly studied theta rhythm recorded in the human EEG and one for which some relationships with behaviour and drug actions have been established. The link was made to hippocampal theta in animals because substantial research and theory regarding this rhythm is available from the behavioural to the intracellular level. Rodent hippocampal theta provides an, often cautionary, model for interpreting the nature

and functional role of FM-theta. Comparison with it also allows a preliminary assessment of whether FM-theta is directly related to theta generated by the hippocampus—with at least some FM-theta proving to be clearly unrelated or at least pharmacologically inversely related. We can now attempt to address some more general questions about FM-theta.

8.1. Possible theories of FM-theta

In this section, we will briefly summarise some theories that provide potential functional accounts of FM-theta. We restrict our discussion to full scale theories: accounts of detailed mechanisms; based on integration of large volumes of data; and where, in the assignment of "function", the theorist is more often focusing on a unitary computational mechanism than on any unitary cognitive function. These should be distinguished from functional hypotheses (e.g. "FM-theta is involved in working memory") that are often reformulations of observed correlations.

8.1.1. Theory—general considerations

The bulk of the work on FM-theta has been correlational. Changes in power have usually been measured simply in relation to changes in task events or responses. In relating these results to theory we must not only be aware that correlation does not entail cause but also that, with rodent hippocampal theta, quite tight and detailed relations of frequency with behaviour are not indicative of functional involvement. One of the strongest correlates of the occurrence of hippocampal theta in rats is movement (walking, running—with the frequency of theta being tightly related to the extent of movement); yet this is not a strong correlate in other species and, more importantly, total hippocampal lesions do not alter walking and running behaviour in rats. For many such cases, then, it can been argued that the simple presence of theta in the hippocampus is unrelated to functional output, despite the fact that when there is functional output theta is important for correct hippocampal function (Gray and McNaughton, 2000).

While theories should not contradict the observed correlations, they can postulate functions that are not tightly linked to them. Critically, functional theories of FM-theta, that is theories that do not simply treat theta as an epiphenomenon, must: (a) attribute some function to the underlying neural rhythmicity itself (see Section 8.2); (b) indicate or imply to what extent, if any, FM-theta is related to hippocampal theta (see Sections 8.3 and 8.4); and (c) involve extensive, likely recursive, neural processing—since theta is cyclical with the length of any one cycle being equivalent to a simple reaction time.

8.1.2. Loop selection and context encoding

In his highly detailed book, Miller (1991) expounded a view of theta as the basis for "cortico-hippocampal interplay and the representation of contexts in the brain". His exposition is particularly important, here, for two reasons. First, he sees the role of hippocampal theta as being, if anything, more the control of isocortex than hippocampus; and says that "the area of isocortex most strongly linked with the hippocampal formation is the part which is spatially most remote from it (the prefrontal cortex)" (p. 217). His theory is, thus, a theory of frontal theta as much as of hippocampal theta. Second, he provides a comprehensive picture of circuitry and resonance. This picture must be accommodated by any theory of theta even if the theory does not accept his suggestion that the function of theta is to represent contexts in the brain—where "each pattern of resonant circuitry is specific to the environment which triggers it into activity, and thus represents the environment, when conventional cell assemblies could not" (p. 220).

The basis for the theory is the anatomical identification of a variety of recurrent circuits of varying length that pass through the hippocampus (and have unidirectional flow at this point, arriving via the entorhinal cortex but not immediately returning there) and can be "selected" by the frequency of theta.

> "Loops of axonal connections between hippocampus and isocortex convey circulating neural activity which resonates with defined phase relations to the theta rhythm concomitantly generated by the hippocampus. These loops are capable of organising themselves, by selection from a larger substrate of axonal connections with the same loop configurations. The selection process involves strengthening of specific connections by rules such as those envisaged by Hebb. Self-organisation is possible because the axonal connections from which these loops are selected for strengthening have very long conduction delays around the loop, which can approximate to the period of the hippocampal theta rhythm. ... According to this theory, contexts are not innate, and are not simply representations of Euclidian space or any other simple topographic mapping of the physical environment. They are acquired to match the total information structure of the environment, and thus are much more flexible in their scope than spatial representations. Amongst the realms of information-processing which can be coordinated by these hippocampally derived contexts, are the many dimension of human thought. ... The overall concept of the hippocampal complex is thus as one of the information processors which organizes, coordinates and indexes information stored in the isocortex; but the hippocampus is not the primary repository of that stored information, this being the much larger cortex itself." (pp. 219–221)

The key neural elements of Miller's theory are: the repetitive, recursive, circulation of information around neural loops; and the variation from occasion to occasion of which circuits are active and which are not. More hypothetical, but still generalizable to other theories, is the proposal that theta frequency controls which cortical circuits are in play. His emphasis on the encoding of context by such circuit selection is more specific and more driven by perceived functions of the hippocampus than of the isocortex. Critically, for his theory to account for very large numbers of contexts, it would seem to imply that theta selects circuits within a neural area to represent a specific context more than it selects, globally, between cortical areas—although loop times are likely to differ more between areas.

8.1.3. Recursion as "figure-ground" resolution of goal conflicts

Gray and McNaughton (2000) accept the fundamental neural architecture of Miller's theory, and the notion of recursion, but: (a) see theta frequency as less a means of selecting circuits and more a means of controlling the quantization of computations; and (b) see changes in theta frequency as affecting the resolution of conflicts between goals rather than of the processing of the context in which a goal might be recognised.

Their theory is quite extensive (with 400 pages of printed text and the same volume of web-based appendices) but most focuses on the hippocampus and the critical issues for FM-theta can be summarised briefly. Gray and McNaughton use, as an analogy, a computational model that is designed to solve the "figure-ground" problem in global stereopsis: the phenomenon whereby people who look at random dot stereograms for long enough can perceive images simply by some process in the brain decoding the angular disparities between sets of dots. The precise details of this computational model are not important (and are not supposed to be instantiated, or even paralleled, by hippocampal circuitry)—but

the key point is that the computer program solves the problem by feeding the output from one computational cycle back into the network as input to the next computational cycle. This is something that the recursive circuitry described by Miller can clearly do. Critically, the solution to the global stereopsis problem arises as a result of this recursive processing over many computational cycles (taking 30 s–1 min in people with normal visual function). This shows that a massive computation can be carried out in very limited circuitry—provided there is sufficient time for the requisite number of computational iterations.

On this theory, theta is fundamentally an inhibitory pacing mechanism—ensuring that the processing of one computational cycle is cleared from the hippocampal circuits before, and so does not degrade, the return of the information from the cortex on the next computational cycle.

The link with goal conflict processing is not made via theta itself. Indeed, a key point for our current purpose is that quantization of recursive processing could be an important general feature of a wide range of quite distinct neural or cognitive processes. The function of theta in the hippocampus derives instead from their assumptions about the information being processed by the hippocampus—and by their view that its main function is as a comparator and integrator of goals. (In their model, "place cells" do not indicate places but represent efference copies of the detection of available goals by the cortex.). So, theta is required for correct hippocampal function, at least when the computational problem is hard to solve, but the cognitive functions of theta in the hippocampus derive from the cognitive functions of the hippocampus (and of its required interactions with, e.g. prefrontal cortex). The function of theta itself, within their theory, is simply to increase the acuity, or extend the range, or increase the speed of such functions as the hippocampus performs as a result of its specific input and output connections. Such improved functionality could be the role of theta-like rhythmicity in any process of any type that required recursion.

However, the core function they attribute to the hippocampus is also of significance for our understanding of FM-theta. They propose that the hippocampus controls behavioural inhibition. This is achieved via an increase in negative cognitive bias (with the increase being potentially progressive over a number of theta cycles). With excess hippocampal function, therefore, they predict increased suppression of behaviour leading to negatively affective consequences via an increase in negative affect and, specifically, anxiety (potentially linked to the personality factor of neuroticism). With insufficient hippocampal function, they predict a failure to suppress incorrect alternatives and so, via a failure to decrease interference from competing associations, the mnemonic problems that characterise "amnesia". They see amnesia not as a failure to store and retrieve correct information but an excess storage and retrieval of conflicting incorrect information that produces a pandemonium that blanks out retrieval of the correct information (McNaughton and Wickens, 2003).

The key foundation of the theory is that all clinically effect anxiolytic drugs so far tested reduce the frequency of hippocampal theta—and there is at least preliminary evidence that drugs that increase theta frequency or power are precognitive (McNaughton et al., 2007). This will be important when we attempt to integrate the existing theories of theta function with what is known about FM-theta.

8.1.4. Phase as an index to spatial, episodic and semantic context

Buzsáki (2006) places theta in the context of, and as one of the centre members, of a set of at least 10 frequency bands spanning 0.05–600 Hz—with each oscillation class, although partially over-lapping others in frequency range, depending on a distinct neural mechanism (Buzsáki and Draguhn, 2004). Further, the relationship of the mean frequencies of the bands is such that "the phase of coupled oscillators of the various bands will vary on each cycle forever, resulting in a non-repeating, quasi-periodic or weakly chaotic pattern: this is the main characteristic of the EEG" (p. 113). Each frequency band quantises processing of different pools of neurones. The main purpose of this is to eliminate the processing problems that would otherwise arise from the very variable timing of arrival of impulses. "The wave length of the oscillatory category determines the temporal windows of processing and, indirectly, the size of the neuronal pool involved. It follows from this speculation that different frequencies favour different types of connections and different levels of computation. In general, slow oscillators can involve many neurons in large brain areas, whereas the short time windows of fast oscillators facilitate local integration, largely because of the limitations of the axon conduction delays. … [suggesting] that the several oscillatory classes have distinct mechanisms, each serves a different function, and each involves various magnitudes of neuronal pools." (pp. 115–117).

It should follow from this view of rhythmicity that the processing of incoming information should be favoured at the local wave peak; and that important stimuli should reset the phase of the rhythm to ensure optimal processing. This appears to be true for cortical alpha and theta as well as hippocampal theta (Buzsáki, 2006, Cycle 6).

Buzsáki (2005, 2006) sees rodent hippocampal theta as allowing navigation through both the external world and episodic memory. He notes that, unlike other brain rhythms, rodent hippocampal theta is sustained for long periods of time. He, along with others, sees the phase precession of firing of hippocampal place cells (O'Keefe and Recce, 1993) as essentially indexing the position of the rat. A critical point, in contrast to Miller's view, is that increased theta frequency (when the rat is running faster) "compensates for the shorter time spent in the place field, leaving the relationship between phase and spatial position unaltered" (Buzsáki, 2006, p. 323).

Thus, despite variation in speed of movement, theta allows the animal's behaviour to occur (and memories to be stored) in a particular context. "Information about places and distances is not determined simply by single assemblies bound to the troughs of theta oscillations but also by the precise temporal sequences within cycles. The sequences within cycles precisely reflect the past, present, and future … [so] the currently coded item is place into *spatiotemporal context* by the theta oscillation mechanism." (Buzsáki, 2006, pp. 326–327).

Such contextualization can occur within episodic and semantic as well as three-dimensional space. "Analogous to the dead reckoning-to-map transition in the rat, exemplified by the conversion of unidirectional to omnidirectional neurons, multiple episodes with a common item can free the common item from its spatiotemporal context. … Episodic and semantic memory representations may have evolved from mechanisms serving dead-reckoning and map-based navigation, respectively." (Buzsáki, 2006, pp. 332–333).

8.1.5. Common features of the theories

We have considered only a few theories (chosen for their expositions in books for which theta was central) and the most important common feature to note about our summaries is our reduction of hundreds of pages of text to a few paragraphs in each case. There is a great mass of details summarised in each case (with substantial overlap in the data covered by the three theories) and the theories differ more in how they make predictions than in the

predictions they make. For example, in the memory domain Buzsáki (like most other current theories that differ from his in the function they propose for the hippocampus) sees the hippocampus as promoting the storage of correct information, whereas Gray & McNaughton see it as preventing the storage of interfering information. Both see the cortex as the ultimate repository of information that ultimately becomes independent of the hippocampus—Buzsáki via a transfer process and Gray & McNaughton since they view the cortex as where both correct and incorrect memory traces are stored from the start, with the hippocampus not being needed once incorrect ones have been sufficiently suppressed. Miller's view is intermediary. He sees the hippocampus as controlling the processing of context but via an indexing system that controls cortical storage of information. Likewise, in relation to context, Miller sees theta as selecting particular circuits via loop round trip times and Buzsáki sees phase as more important (with changes in theta frequency maintaining the same phase context) but, in both cases, an artificial change in frequency would disrupt processing and in both cases theta phase is important for the control of neural plasticity via long-term potentiation and depression. Gray and McNaughton, in partial contrast, emphasise that the hippocampus is involved in innate as well as learned reactions and would see it as involved in some simple (e.g. approach-avoidance) reactions as well as complex ones. But, in the memory domain, their theory is fundamentally linked to interference and, in many cases what is viewed as context by the other theories will create interference (see Gaffan, 1994).

It is difficult, then, to extract from the theories a single, clearly more correct, view of the cognitive functions of hippocampal theta. For that reason, and given the paucity of equivalent detailed neural data, we will not attempt to adduce an equivalent theory for FM-theta.

However, if we look at the general style and architecture of theories – and, in particular, their views of hippocampal-cortical interactions and of possible other theta-related neural interactions – we can extract a number of essentially common general principles. These are likely to hold for, or at least be useful in the construction of, any future detailed theory of FM-theta.

- Theta is seen as a means of controlling the passage of information around multiple cortical loops, and principally is a solution to the problem of variation in loop delay times. This could select particular circuits on the basis of their tuning to the current frequency (Miller); select circuits that require a particular intermediate processing time (of the order of a theta cycle) to complete and return their computations (Buzsáki); or simply quantise information passing round circuits tuned to the current frequency to assist recursive processing (Gray and McNaughton).
- The key cognitive functions supported by theta require long-term processing. For tuning or recursion to operate, the time taken to reach a final solution by the circuits involved requires multiple theta cycles and so, potentially, operates on the time scale of a second or more.
- Hippocampal theta is distinct from cortical theta. It tends to be sustained and its influence only escapes into cortical areas occasionally. Provided what we are seeing in the cortex is coherent with the hippocampus it indicates functional interaction of the hippocampus with cortex.
- Theta resulting from hippocampal-cortical interactions is important for the processing of complex memories. This conclusion needs to be treated with caution as (a) the underlying function could be important for non-memorial processing as well as memorial; (b) this need not be true of theta generated cortically and without any interaction with the hippocampus; and (c) there

is no general agreement as to the type of memory supported by the hippocampus (see Gray and McNaughton, 2000, Chapter 8).
- Phase and phase reset will be important for processing and, simply as a consequence of the related changes in membrane potential, will affect information storage via long-term potentiation and long-term depression.

8.1.6. Theoretical issues for FM-theta

There are a number of questions raised for our review of the data on FM-theta by our consideration of these theories. Does FM-theta have functional significance? Is FM-theta related to hippocampal theta? What are the similarities and differences between FM-theta and hippocampal theta? The theories we have considered are primarily theories of hippocampal theta—although all necessarily have implications for cortical processing (with Buzsáki having the strongest focus). It is only in answering these questions that we can see how far our current understanding of hippocampal theta can inform theories of FM-theta.

8.2. Does FM-theta have functional significance?

Until recently, it could be said that "despite extensive work on the behavioural and physiological correlates of brain rhythms, it is still unresolved whether they have any important function in the mammalian cerebral cortex" (Sejnowski and Paulsen, 2006). However, at least with hippocampal theta, it has now been demonstrated that rhythmicity, in and of itself, is functional (McNaughton et al., 2006).

The correlational work, if taken at face value, suggests that FM-theta is involved in memory (Gevins et al., 1998, 1997) and emotional processes. In particular there is a clear link between the presence of FM-theta and working memory tasks. Furthermore, the amount of FM-theta is correlated with task difficulty or working memory load, sustained practice, and successful performance. FM-theta occurs during a number of different types of memory tasks, using a variety of modalities. In addition, FM-theta has been noted during encoding, rehearsal, and retrieval. This suggests that FM-theta has a non-specific function such as sustained attention necessary to perform a working memory task rather than being a feature of the processing of working memories themselves.

There may also be different functions for different occurrences of FM-theta. Deiber et al. (2007) suggested that the brief theta components occurring following stimulus presentation may be important for attention, whereas the later components during the delay period could be important for working memory, or more specifically active rehearsal. Missonnier et al. (2006) found that FM-theta was also greater following stimulus presentation in an attention condition than an N-back 2 condition. This suggests different allocation of attentional resources in the N-back versus attention conditions and a role for theta in attention.

Questions can also be raised about the linking of theta to functions regularly performed within any task. Onton et al. (2005) reported that FM-theta increased on only a relatively small percentage of trials. This sporadic nature of FM-theta, coupled with the research suggesting that it is present in only some types of individuals' EEG suggests that it is not linked to any regularly executed function. However, it is possible that FM-theta is normally much lower in amplitude or poorly and irregularly transmitted to the surface, so as to be undetectable using current methods, in most individuals.

Although direct manipulation of FM-theta has not been attempted, links with specific biological manipulations or factors provide some indication of genuine functional involvement. Anxiolytic medications, including the pharmacologically distinct classes of benzodiazepines and buspirone, increase FM-theta. This

has been typically observed during the performance of working memory or sustained attention tasks. Consistent with these drug data, increased FM-theta also correlates with lower levels of anxiety and neuroticism, and higher rates of extraversion. Mizuki et al. (1994) noted that buspirone only increased FM-theta and concurrently reduced STAI-S scores in a group selected based on the initial presence of FM-theta. Thus, the effectiveness of the drug on a behavioural measure appeared to be linked to the endogenous state of the theta system—arguing for functional involvement of theta in behaviour. These data all suggest that FM-theta could be involved in the modulation of anxious states.

In summary, correlational approaches suggest that FM-theta is importantly involved in working memory and/or sustained attention on the one hand; but that it is increased by anxiolytic drug action and personality-related reductions in anxiety on the other. These results are superficially paradoxical. However, we should note that FM-theta is most obvious with well-trained participants in cognitive tasks—when task-related arousal is likely to be reduced and attentional resources focused. The meditation data make it possible that FM-theta is a sign that attentional resources are more internally than externally focused.

8.3. Is FM-theta related to hippocampal theta?

A primary question that arises is to what extent FM-theta could be connected to the hippocampus and other regions of the brain. Can it, as is suggested by the current animal data, sometimes reflect and be coherent with activity in the hippocampus for certain functions and at other times lie dormant while the hippocampus is active in the theta range, and vice versa? Furthermore, is the phase of FM-theta important for the encoding or recall of information, since phase differs between encoding and retrieval (Rizzuto et al., 2006), as has been shown with rodent hippocampal theta? Thus far, phase reset has been shown during a working memory task, during encoding and retrieval, in the rodent.

The frontal lobe has a number of connections with the hippocampus, the ACC, and other cortical regions. There are now several studies that have demonstrated a link between frontal EEG activity and hippocampal activity in rodents (Jones and Wilson, 2005; Siapas et al., 2005); and a recent human study has shown that the level of glutamate within the hippocampus influences frontal-theta (Gallinat et al., 2006). Recent data from our laboratory (Young and McNaughton, 2008) suggest that there are two frontal theta bands in rodents—a generally lower one not linked to hippocampal theta and a generally higher one during which coherence with the hippocampus is high. In this review, both because of conventional data reporting and because of apparent functional distinctions between theta and alpha, we have restricted our analysis to 4–8 Hz, the traditional theta range. In rodents, hippocampal theta is often in this range but can range from 4 to 12 Hz. Similarly, activity directly recorded from the human hippocampus has been reported with frequencies ranging from 3 to up to 16 Hz (Arnolds et al., 1980a; Ekstrom et al., 2005; Rizzuto et al., 2003). Thus, functional relationships are likely to exist between the hippocampus and FM-theta but the links may be frequency-dependent (with lower frequency FM-theta potentially being unrelated to hippocampal activity) and sporadic.

8.4. What is the source of FM-theta?

At present MEG studies suggest that the ACC could be involved in the generation of FM-theta. ACC appeared to contain the strongest source of frontal-cortical theta in rats (Young and

McNaughton, 2008). This would make sense given that the ACC is associated with both emotional and cognitive phenomena (Devinsky et al., 1995). Also there is evidence of the ACC subregions subserving multiple distributed attentional systems (Peterson et al., 1999). This would indicate that the ACC, frontal cortex, and hippocampal regions are potentially functionally related. Furthermore, there are known connections between the septo-hippocampal system and the ACC. Thus, the ACC could potentially be the generator of FM-theta or could possibly relay theta from other sources including the hippocampus.

Having said all that, the localization data are inconclusive, and it could be argued that multiple bilateral sources could explain much. Kahana et al. (1999) recorded theta rhythms from almost everywhere on the cortex during virtual navigation. This would probably sum to a vertex maximum—but would this task generate FM-theta? This probably requires more MEG studies, more intracranial recordings, some fMRI and carefully chosen paradigms. Studies involving intracranial EEG also need to use concurrent scalp EEG to better determine the relationship between theta recorded from the hippocampus and frontal regions.

Coherence studies are also starting to demonstrate coupling between FM-theta and theta recorded at other brain sites. The data appear to fit with Miller's (1991) and Baddeley's (1986); Baddeley and Hitch (1974) conceptualization of working memory as involving recursive connections. It is unlikely to be volume conducted directly from the hippocampus to Fz. The MEG studies and source analyses indicate a more frontal source (or sources), but do not localise it definitively. Furthermore, Cantero et al. (2003) demonstrated an absence of theta coherence between cortical and hippocampal electrode sites during awakening and while awake. All of this adds up to the likelihood that FM-theta is not a volume conducted projection of hippocampal theta.

8.5. How could FM-theta interact with hippocampal theta?

In this regard, it is generally assumed that coherent theta in neocortex and hippocampus is due to interaction via the entorhinal cortex (EC), and certainly this is the pathway proposed by Miller (1991) for theta-modulated cortico-hippocampal resonant loops. It has been pointed out however (Kirk and Mackay, 2003), that theta-modulated activity is seen in cells of the input layers of the EC (i.e. in the EC relay from neocortex to hippocampus), but not in the cells of the output layers (i.e. in the EC relay from neocortex to hippocampus). Thus, in part, neocortical theta (including frontal-midline theta) may indicate that a neocortical to hippocampal input pathway is currently active. The finding that theta activity in medial prefrontal cortex preceded theta activity recorded from CA1 in the hippocampus (Jones and Wilson, 2005) is consistent with this view.

As cells in the hippocampal output layers of the EC relay are not theta modulated, the hippocampal to cortex part of a recurrent cortico-hippocampal loop proposed by Miller (1991) is probably not via the most direct route via the EC. However, Kirk and Mackay (2003) also note that the theta-modulated re-entrant loop might be completed via descending projections to the medial mammillary bodies, and back to neocortex via the anterior thalamic complex. In humans, the anterior thalamus has projections to both frontal and temporal neocortex (Behrens et al., 2003). Furthermore, coherence in the theta band has been demonstrated between the thalamus and cortex during a calculation task (Sarnthein et al., 2005). Thus, neocortical theta (including frontal midline) may also indicate that an output pathway from the hippocampus is currently active. The neocortical input and output parts of the cortico-hippocampal loop may operate simultaneously in some circumstances and independently in others.

8.6. Similarities and differences between FM-theta and hippocampal theta

There are a number of similarities between FM-theta and hippocampal theta. FM-theta, as conventionally, defined and hippocampal theta (defined as sinusoidal rhythmical slow activity recorded from the human hippocampus), are both within the same general frequency range—although both human and rat hippocampal theta appear to extend above the conventional FM-theta range. An FM-theta like rhythm has been noted during REM sleep, which has continuous hippocampal theta. Both FM-theta and hippocampal theta can also be elicited by sustained attention tasks. Following the administration of drugs such as anxiolytics both FM-theta and hippocampal theta change.

However, anxiolytic drugs tend to produce an increase in the amount of FM-theta activity in humans and a decrease in the amount of theta activity in rodents. Similarly, an FM-theta-like rhythm occurs not only during REM sleep but also during stage 1 sleep, which does not have hippocampal theta.

There are also a number of more fine-grain differences between FM-theta and hippocampal theta activity. Human FM-theta studies typically report changes in spectral power for a certain frequency; whereas animal hippocampal theta studies more often report shifts in peak frequency in response to any task or drug. This difference may be more methodological—driven by the type of measurement made. Certainly, in electrophysiological studies of rat hippocampal theta, amplitude (or power) tends to reduce when frequency reduces—and so power changes certainly occur. However, the contrast here is with a general lack of reported frequency changes in human studies—although this could be the result of the general use of Fourier transform. Changes in rat theta frequency are usually calculated over a few theta waves (since frequency decays rapidly after the onset of stimulation) from the inter-peak intervals. Changes produced by drugs at behaviourally relevant doses are typically a reduction of between 0.5 and 1.0 Hz relative to control. Over a sampling time during which ongoing behaviour can be treated as static, or over which electrical stimulation produces it's clearest voltage-related effects, i.e. about 0.5 or perhaps 1.0 s, a Fourier transform can only resolve frequency to ± 1.0 or ± 0.5 Hz, respectively. This methodological issue needs to be dealt with in future research—possibly through a greater focus on wavelets and related approaches.

In humans, where clear FM-theta can be observed in the raw EEG, it tends to wax and wane during tasks; whereas rodent hippocampal theta is more or less continuous and has much less variation in amplitude for a given frequency. Here source may be the critical issue. In rats, frontal and cingulate theta can show equivalent waxing and waning. Similarly, while the hippocampus shows extensive theta, this is only occasionally coherent with frontal activity (Young and McNaughton, 2008). Comparison of direct frontal and hippocampal recordings in humans would be useful here; but it is difficult to envisage the conditions under which this could be achieved given the normal limitations on clinical recording.

The implication of the animal data, that frontal and hippocampal theta show at the best only partial overlap is supported by the general pattern of results in humans. Tasks that might be expected to elicit some form of FM-theta (such as mental arithmetic and REM sleep) have not elicited a clear theta component in hippocampal recordings. Conversely, tasks (writing and walking) that were reported to modify hippocampal theta in one subject (Halgren et al., 1978) would probably not elicit FM-theta.

If FM-theta is not related to hippocampal theta, the question arises as to whether theta recorded from other locations could be possible candidates. For example, Brazier and Casby (1952) demonstrated rhythms that would fit our definition of FM-theta, but also identified a slightly faster distinct temporal rhythm of 7–8 Hz, in some individuals during mental calculation. Furthermore, Vogel et al. (1968) identified a posterior rhythm of up to 7 Hz during difficult subtractions. In addition spatial navigation tasks and some working memory tasks produce theta activity over temporal and parietal regions.

8.7. Main conclusions and future directions

In conclusion FM-theta, like hippocampal theta, appears to play a role in (or at least occur during) processing of memory and emotion. But, like and even more so than hippocampal theta, the nature of its role is unclear and definitive evidence for functional involvement in cognitive or emotional processing is lacking.

One possible solution to this problem is animal research. Research is starting to examine theta recorded from frontal sites in monkeys and rodents. If FM-theta can be shown to have similar correlates in these animals; this would allow an animal model of FM-theta to be developed. Lesion studies, and techniques such as the "brain bypass" could then be conducted to examine the source and relatedness to hippocampal theta alongside its function. However, the animal and human literatures tend, currently, to use disparate paradigms. The testing of humans in non-verbal paradigms – and care in dealing with species-specific reactions and variations in task difficulty – will be needed if homology is to be firmly established.

The issue of sporadicity and low incidence also needs to be addressed further. Clear bursts of FM-theta may only be observable in a tenth or so of the population; and this observability may relate to genuine differences in the incidence or amplitude of intracranial events. However, it seems likely that at least part of the variation in observability results from variation in transmission of currents to the surface. It seems likely, therefore, that it would be useful to determine how far, in those who do not show clear bursts of theta, signal processing methods can show equivalent occurrence and properties of lower amplitude rhythmicity.

Perhaps the most hopeful, but at present least followed path, is pharmacological. Drugs change the EEG and, importantly, functional classes of drugs with quite different primary receptor actions have similar effects. "The EEG can thus be used as a tool to sensitively detect central nervous system changes associated with medications. For example, medications that induce drowsiness will induce characteristic EEG signs of drowsiness whereas those that interfere with the ability to concentrate can affect the attention-related signals of the EEG" (Chung et al., 2002). Within the rat hippocampal literature the pharmacological correlates of theta (McNaughton et al., 2007) have been much clearer than any nominal behavioural ones. Further, drugs have been used to distinguish different classes or types of hippocampal theta (Bland, 1986) and could clearly do the same for FM-theta. More generally, "rhythms are a robust phenotype that can be monitored and quantified objectively for the diagnosis and progression of psychiatric and neurological ailments. ... Rhythms are affected by most psychotropic drugs, and testing their effects on neuronal oscillations will likely become a widespread tool in drug discovery" (Buzsáki, 2006, p. 372).

Both with animal work and human, it is clear that changes in functional connectivity, indicated by changes in coherence, have the capacity to discriminate multiple different functional types of "theta" activity. However, this is as yet an untapped resource with very few studies in rats or humans focusing on this. If rhythmicity in general and theta in particular are means of binding areas into functional circuits (Bland and Oddie, 2001; Buzsáki, 2006; Miller,

1989, 1991) then variations in coherence may be more important than the nominal function discharged by the rhythm in any particular area.

Given the apparent richness of the current data on FM-theta, it would be tempting to conclude a review such as this with a detailed theory, attributing rich cognitive complexity to the rhythmic activity that appears to vary with so many detailed aspects of so many tasks. However, the literature on rat hippocampal theta spent many years wandering in a wilderness of supposition based on correlational work—with none of the hypotheses advanced standing the test of time and, as noted in the introduction, no current agreement. This suggests that the analysis of frontal-midline theta will be best served by careful application of Morgan's cannon—a search for the simplest and most basic process that will account for its occurrence. This should clearly be coupled with attempts to discriminate between different types of "theta"—which may be best via tests of coherence with non-frontal sites, or via drug challenges, than with definitions based on frequency bands.

Indeed, the apparent cognitive richness of the data should perhaps make us attempt theories that see theta more as a class of mechanism than as reflecting a particular function. Theta may be a sign of a particular intensity or level of processing (i.e. the cycle time determines the size of the neural networks that can be engaged in current computations) as suggested by Buzsáki (2006) or of a particular quality of processing such as recursion as suggested by Gray and McNaughton (2000). If this is the case the cognitive function of FM-theta at any particular point in time will depend on which other structures it is interacting with and the different functions fulfilled at different times may be quite distinct in cognitive terms, sharing only a common level or common means of computation.

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