# SHORT COMMUNICATION
# Frontal theta activity in humans increases with memory load in a working memory task

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## Abstract

Recent theoretical work has suggested that brain oscillations in the theta band are involved in active maintenance and recall of working memory representations. To test this theoretical framework we recorded neuromagnetic responses from 10 subjects performing the Sternberg task. Subjects were required to retain a list of 1, 3, 5 or 7 visually presented digits during a 3-s retention period. During the retention period we observed ongoing frontal theta activity in the 7–8.5-Hz band recorded by sensors over frontal brain areas. The activity in the theta band increased parametrically with the number of items retained in working memory. A time–frequency analysis revealed that the task-dependent theta was present during the retention period and during memory scanning. Following the memory task the theta activity was reduced. These results suggest that theta oscillations generated in frontal brain regions play an active role in memory maintenance.

## Introduction

There are numerous reports on the modulation of theta band activity in humans performing episodic and working memory tasks (Burgess & Gruzelier, 1997; Gevins *et al*., 1997; Doppelmayr *et al*., 1998; Kahana *et al*., 1999; Klimesch, 1999; Tesche & Karhu, 2000; Raghavachari *et al*., 2001; de Araujo *et al*., 2002). Theta activity over the frontal midline is particularly strong as measured by electro-encephalography (EEG) and magnetoencephalography (MEG) (Mundy-Castle, 1951; Brazier & Casby, 1957; Mizuki *et al*., 1980; Bruneau *et al*., 1993; Inouye *et al*., 1994; Iramina *et al*., 1996; Takahashi *et al*., 1997; Inanaga, 1998). A study using the 'n-back' paradigm demonstrated that engagement of the working memory (WM) is sufficient for inducing frontal theta activity (Gevins *et al*., 1997). In the *n*-back task, subjects are presented with a continuous stream of items and must indicate whether the displayed item matches the one presented *n* positions back. Since the intervals of encoding, retention and recall of the memory items are not separated in the *n*-back task, it is unclear which components of the task induce the theta activity. Indeed, a recent MEG study demonstrated that the duration of hippocampal theta activity increases with memory demands during the recall period of a WM task (Tesche & Karhu, 2000). Thus, it must be clarified whether frontal theta activity persists during the retention of WM or mainly increases transiently in response to encoding and/or recall. A study applying subdural electrodes in epileptic patients demonstrated that theta activity did persist during WM retention (Raghavachari *et al*. 2001). However, it remains unknown to what

extent the intracranially recorded theta activity contributes to the frontal theta measured by EEG/MEG and to what extent these results generalize to healthy subjects.

The goal of this study was to characterize frontal MEG signals in humans performing the Sternberg task (Sternberg, 1966). In contrast to the *n*-back task presentation, retention and recall are separated in the Sternberg task. MEG responses were analysed to investigate the dependence of frontal theta activity on memory load. A wavelet-based time–frequency analysis was applied to characterize the theta signal in time.

## Materials and methods

### Experimental paradigm

A slightly modified version of the Sternberg paradigm was applied. Each trial was composed as follows: first, the word 'Blink' appeared on the monitor and the subjects were encouraged to make an eye blink. A prompt to start, 'S', appeared 1 s later, followed by sequential presentation of a list of 1, 3, 5 or 7 digits. Each item was flashed on the screen for 0.15 s at a rate of 1.2 s per item. The set size was varied randomly. After a 3-s retention interval (blank screen) the probe was presented. The subjects indicated if the probe was on the list or not by lifting the right and left finger, respectively. Three blocks of 60 trials were presented to every subject. As a control task, all digits were replaced by crosses. Two blocks of 60 trials were presented.

### Data acquisition

MEG data were recorded from 10 subjects (5 males and 5 females, aged 23–37 years; Tesche & Karhu, 2000). Informed consent was obtained from each subject after full explanation of the study. Magnetic signals were measured using a Neuromag MEG system

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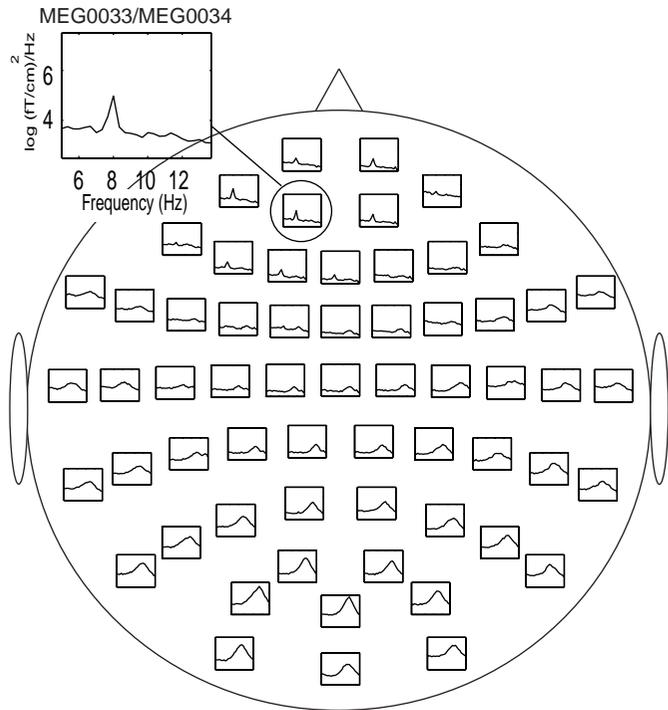
FIG. 1. The averaged power spectra for subject WY calculated during the retention period for all memory loads. The individual figures are arranged topographically according to the corresponding position of the planar gradiometers on the helmet. Spectra from gradiometers with the same location, but orthogonal orientations are averaged.
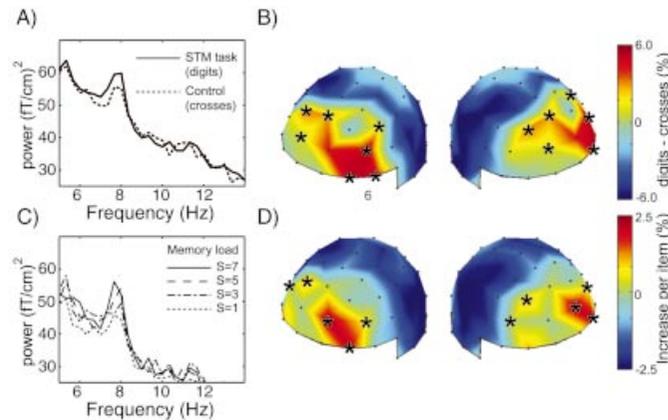


FIG. 2. (A) The normalized and averaged power spectra (retention interval) for the 10 subjects calculated for frontal sensor MEG0033 (the location of MEG0033 is indicated in Fig. 1). The spectra averaged for all memory loads (solid line) show a peak in the 7–8.5-Hz theta band which is stronger for the memory condition (digits, solid line) than for the control condition (crosses, broken line). (B) The relative increase in power for the memory condition (digits, power averaged for all loads) compared with the control condition (crosses), colour coded on a Neuromag helmet seen from top left and top right. Each dot represents the location of two planar gradiometers of orthogonal orientation. The asterisks indicate locations where the theta power in at least one of the gradiometers was statistically significantly stronger for the memory than the control condition (t-test, $P < 0.05$, 8 gradiometers in total). (C) The normalized and averaged power spectra show a systematic increase in the theta band with memory load in frontal sensor MEG0033. (D) The increase in theta power per memory item, colour coded on the Neuromag helmet. The increase was calculated from a measure based on the regression coefficient (see Methods) of 7–8.5-Hz theta power as a function memory load. The asterisks indicate locations where at least one of the gradiometers had a statistically significant regression coefficient ($P < 0.05$, 5 gradiometers in total).
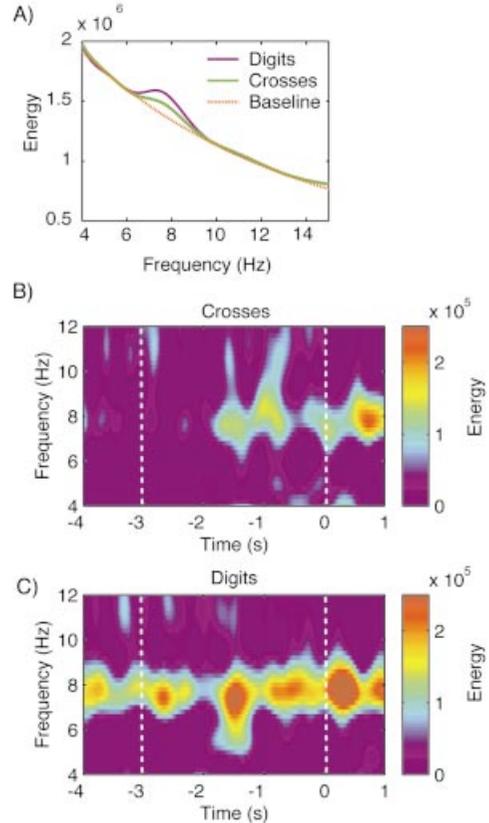


FIG. 3. Time–frequency analysis of the signals recorded from sensor MEG0033, normalized and averaged over the 10 subjects. (A) The time–frequency representations of the energy averaged for time –4 s to +1 s (this measure is quite similar to a power spectrum). The broken line is an exponentially decaying function fitted to the energy values $[E(f) = 10^5(2.4 + 25.5 \ e^{-0.11f})]$. This function is used as a baseline for the time–frequency representations of the energy. (B) The averaged time–frequency representations for the control task (upper panel) and the memory task (lower panel). At time $t = -3$ s the last item in the list is presented and at time t = 0 s the probe item is presented. The colour code represents the energy of the signal with respect to the baseline.

located at the Brain Research Unit, Low Temperature Laboratory, Helsinki. This system has 122 planar SQUID gradiometers at 61 locations distributed over the scalp (Ahonen *et al.*, 1993). The signals were bandpassed at 0.3–130 Hz, digitized at 397 Hz, and then down-sampled to 198.5 Hz.

### Data analysis

Electro-oculographic responses were measured simultaneously with the MEG. Responses in excess of $\pm\,75\,\mu$V were considered to be contaminated by blink artefacts and ignored in the analysis. The power spectra of the raw traces recorded during the 3-s retention interval were calculated using a 600-point fast Fourier transform algorithm. The power spectra for each set size and each subject were averaged across epochs. Prior to averaging over subjects, the power spectra for each memory load were normalized with respect to the total power for load (set size) $S = 1$. The theta band of interest was constrained to the frequency interval in which a clear load-dependent peak was observed. Theta power values from this frequency interval were extracted for the individual trials and subjected to further analysis. For each gradiometer the increase in theta power with respect to set size ($S = 1, 3, 5$ and $7$) was fitted to the expression

$P_\theta(S) = a\,S + b$, where $b$ is the intercept and $a$ the regression coefficient (slope). The relative increase in theta power per item (%) with respect to memory load $S = 1$ was defined as:

$$P_{\mathrm{inc}} = 100 \times (a\ +\ b)\cdot.$$

This measure was then tested for statistical significance using a nonparametric method: the power values for the individual trials were randomly shuffled for S = 1, 3, 5 and 7, and $P_{\mathrm{inc}}$ was then calculated again. This procedure was repeated 1000 times. The statistical significance of $P_{\mathrm{inc}}$ was determined from the distribution of the shuffled values . This shuffling procedure was applied to theta power values for the individual trials combined for all 10 subjects. When comparing the memory (digits) with the control condition (crosses), the 7–8.5-Hz theta power values for the individual trials were combined for the two conditions from the 10 subjects and compared using a $t$-test.

Time–frequency representations were calculated by Morlet wavelets (Sinkkonen et al., 1995; Tallon-Baudry et al., 1996). The energy $E(t, f_0)$ at time $t$ and frequency $f_0$ is given by the squared norm of the convolution of the signal $s(t)$ to a Morlet wavelet,

$$w(t, f_0) = A\,\exp(-t^2/2\sigma t2)\,\exp(2i\pi f_0 t),$$

i.e. by:

$$E(t, f_0)\ =\ |w(t, f_0)\ \times\ s(t)|^2 \tag{1}$$

where $\sigma_f = 1/2\pi\sigma_t$ and $A = (\sigma_t\sqrt{\pi})^{-1/2}$. The 'width' of the wavelet $m = f_0/\sigma_f$ is given the value 7. The time–frequency representations were calculated for individual trials and then averaged. An exponentially decaying function was fitted to the time–frequency representations averaged over time (see Fig. 3A). This function was then used as a baseline in the time–frequency representations shown in Fig. 3C.

## Results

Behavioural responses were characterized by reaction times. The reaction time increased with a slope (regression coefficient) of $51 \pm 6$ ms per item. The subjects performed the task with few errors (4.5% on average). The slopes were steeper than those reported in the original Sternberg experiment (Sternberg, 1966) probably because of the differences in the experimental setup, such as the longer retention period and the lack of feedback after answering. Nevertheless, the fundamental finding of the Sternberg experiment was reproduced; there was an increase in reaction time with memory load (Sternberg, 1966).

The power spectra were calculated for the individual trials from the MEG recorded during the 3-s retention period and then averaged. Figure 1 shows the power spectra for subject WY topographically arranged according to the coil positions on the MEG helmet. The spectra for planar gradiometers with the same location, but orthogonal orientations were averaged. A spectral peak in the 10–12-Hz alpha band is observed in sensors located over the back of the head and a 7–8.5-Hz peak in the theta band is observed over frontal areas. In this paper we concentrate on the frontal theta activity; see Jensen et al. (2002) for an investigation of the alpha activity in a related WM task.

The power spectra for frontal gradiometer MEG0033 (location indicated in Fig. 1) averaged over the 10 subjects for all the memory loads (digits) and the control task (crosses only) are shown in Fig. 2A. The power of the 7–8.5-Hz theta activity was significantly stronger for the memory condition than the control task. Since a clear peak is observed in the 7–8.5-Hz band which varies with memory

demands, the subsequent data analysis will focus on this frequency band. Figure 2B represents the relative change in 7–8.5-Hz theta power colour-coded on the Neuromag helmet when comparing the memory condition with the control condition. The asterisks indicate locations in which the increase was statistically significant ($P < 0.05$) in at least one of the orthogonal gradiometers. Clearly, the increase is dominant over frontal regions. As shown in Fig. 2C, the spectra averaged over the 10 subjects revealed a systematic increase in 7–8.5-Hz theta power with respect to memory load (S = 1, 3, 5 and 7, Fig. 2C). The colour-coded Neuromag helmet in Fig. 2D represents the relative change in 7–8.5-Hz theta power with memory load per item calculated from the regression coefficient (see Materials and methods). Gradiometer locations with a significant increase ($P < 0.05$) are marked with asterisks. Again the increase is observed over frontal regions. Interestingly, there appears to be a decrease in 7–8.5-Hz theta power over central and posterior brain regions. However, since no distinct peak in the theta band was detected in the power spectra over these regions we did not subject this observation to further analysis. In Fig. 2B and D there is a small indication of two separate regions showing significant theta band increase with load. Due to the relatively poor signal-to-noise ratio we cannot establish if this separation is real. Note that, even though the increase in theta power is observed in a relative low number of gradiometers (8 and 5 for Fig. 2B and D, respectively), this effect is unlikely to be explained by Type 1 errors when evaluating the significance in the 122 gradiometers. First, the gradiometers measuring a significant increase are either next to each other or close by, so they probably detect a theta signal from a common source. Secondly, the central and posterior gradiometers show a decrease in the 7–8.5-Hz theta power with memory load, thus constraining the relevant set of gradiometers to be tested to those over the frontal region.

The temporal characteristics of the frontal theta activity was investigated by a wavelet-based time–frequency analysis. The representations were averaged over all memory loads (digits) and all control trials (crosses). Figure 3A shows these time–frequency representations averaged over time. Since the energy decays as a function of frequency, colour-coded time–frequency representations will only reveal lower frequency bands. We have therefore corrected the time–frequency representation with respect to an exponentially decaying function fitted to the energy as a function of frequency (broken line in Fig. 3A). In Fig. 3B, the averaged time–frequency representations for the control and memory task are shown for the signal recorded by sensor MEG0033. In the control task some theta activity is observed in the second half of the retention period. In the memory task theta is observed throughout the retention interval (Fig. 3C). Also a strong patch of theta is observed during recall.

## Discussion

We have utilized whole-scalp MEG recordings to characterize human frontal theta activity during maintenance and recall in the Sternberg task. The main result was a parametric increase in 7–8.5-Hz theta power with memory load during memory retention, and stronger theta activity in the memory task compared to a control task. The memory-dependent theta power was observed in planar gradiometers (sensors) located over frontal brain areas. A time–frequency analysis revealed that the theta activity remained strong during the retention interval, and appeared particularly strong following the presentation of memory items and the probe.

The frequency limits of the theta band have been differently defined in various studies. In rats, the hippocampal theta frequency

changes continuously with behavioural parameters and is often defined from 6 to 10 Hz (Ekstrom *et al.* 2001). In humans the theta component is typically defined from 4 to 8 Hz (Kahana *et al.* 2001). However, with intracranial recordings, the theta oscillations were identified in the interval from 4 to 9 Hz (Raghavachari *et al.* 2001). Thus, the WM-dependent theta activity peaking at ≈ 8 Hz reported in this study belongs to the high end of the theta band.

Our findings are reminiscent of several other reports describing theta activity in humans performing WM tasks. In an EEG study, Gevins *et al.* (1997) reported an increase in frontal theta with task difficulty, in subjects performing the *n*-back task. From this study it was not clear if the increase in theta activity correlated with encoding, retention or recall. In addition to the findings of Gevins *et al.* (1997), we have been able to show that: (i) the theta activity increases parametrically with memory load and (ii) the theta activity is sustained during the retention period.

One interpretation of the increase in theta activity with memory demands, consistent with the traditional view, is that the increase reflects enhanced attention (Mizuki *et al.*, 1980; Bruneau *et al.*, 1993; Gevins *et al.*, 1997). The concept of attention in the context of WM deserves to be better defined. We propose that the increase in frontal theta with memory load is a consequence of sustained neuronal activity reflecting active maintenance of memory representations.

Models exploring the possible functional role for theta in WM maintenance and recall have previously been proposed (Lisman & Idiart, 1995; Jensen *et al.*, 1996; Jensen & Lisman, 1998). In these models, up to 7 items are sequentially activated within a theta cycle. The framework is consistent with the idea that different memory representations are encoded by firing in different phases of the theta cycle. The sequential activation of memories explains the linear increase in reaction time with memory load during memory scanning. Two different versions of the models have been further developed which can account for the full reaction time distribution of the Sternberg task (Jensen & Lisman, 1998). In one version, the adapting theta model, the theta frequency was predicted to decrease with memory load. In this study we have found no evidence of such a phenomenon. Consistent with our findings, the second version of the model predicts the theta frequency to remain constant with memory load, and the amplitude to increase with load.

Several EEG studies have reported changes in the power of the theta band during encoding and recall of episodic memory (Klimesch, 1999); however, these findings were not restricted to frontal theta activity. Future research is required to investigate the relationship between the frontal theta observed in WM paradigms and the changes in the theta band in episodic memory tasks.

What brain regions are responsible for producing the load-dependent theta activity? Multiple functional neuroimaging studies have demonstrated that areas in frontal cortex are engaged in the maintenance and recall of WM representations (for an extensive review see Owen, 2000). Previous MEG and EEG studies have found a source for frontal theta activity in the anterior cingulate cortex (BA 24 and 43; Iramina *et al.*, 1996; Gevins *et al.*, 1997; Ishii *et al.*, 1999). In a recent study, combining EEG and MEG, additional theta sources were found in medial prefrontal cortex (Asada *et al.*, 1999). These source locations are consistent with several functional magnetic-resonance imaging and positron-emission tomography studies which identified the same brain regions as being involved in WM maintenance and recall (Cohen *et al.*, 1997; Petit *et al.*, 1998; Smith & Jonides, 1999; Rowe *et al.* 2000). Thus, the memory-dependent frontal theta activity characterized in this work is possibly generated by some of the prefrontal areas, which have been found to be involved in WM in PET and fMRI studies. The lack of theta activity increasing with memory load over central and posterior areas by no means indicates that these areas are not involved in WM. For instance, in a Sternberg like study, Sarnthein *et al.* (1998) found that parietal and frontal EEG electrodes measured task-dependent activity, which was coherent in the theta band. It is our hope that current estimates of the oscillatory sources in the frequency domain will help us to identify the memory-dependent theta sources (Jensen & Vanni, 2002).

## Acknowledgements

## Abbreviations

WM, working memory; EEG, electroencephalography; MEG, magnetoencephalography.

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