Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices

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ABSTRACT

Recent evidence has suggested that theta-frequency (4-7 Hz) oscillations around the human anterior cingulate cortex (ACC) and frontal cortex, namely frontal midline theta (Fm theta) oscillations, may be involved in attentional processes in the brain. However, little is known about the physiological basis of Fm theta oscillations, as invasive study in the human is allowed only in limited cases. In the present study, we developed a monkey model for Fm theta oscillations and located the generators of theta waves using electrodes implanted in various cortical areas. Monkeys were engaged in a self-initiated hand movement task with a waiting period. The theta power in area 9 (the medial prefrontal cortex) and area 32 (the rostral ACC) was gradually increased from a few seconds before the movement and reached a peak immediately after the movement. When the movement was rewarded, the theta power attained a second peak, while it swiftly decreased in the unrewarded trials. Theta oscillations in areas 9 and 32 were coherent and phase-locked together. This theta activity may be associated with ‘executive attention’ including self-control, internal timing, and assessment of reward. It is probably a homologue of human Fm theta oscillations, as judged from the similar localization, corresponding frequency, and
dependence on attentional processes. The monkey model would be useful for studying executive functions in the frontal cortex.
INTRODUCTION

Theta-frequency (4-7 Hz) oscillations in the human brain are observed in a large variety of different situations (for review, see Schacter 1977). Although our present knowledge is insufficient to form a generalized theory, recent electrophysiological studies have suggested that some theta oscillations play important roles in the neural processes of memory, cognition, and attention in humans and animals (for review, see Basar et al. 2001; Kahana et al. 2001; Klimesch 1999). It has been established that frontal midline theta (Fm theta) oscillations are involved in attentional processes (for review, see Inanaga 1998). They have been recorded around the frontal midline region of the scalp by electroencephalogram (EEG) (Ishihara and Yoshii 1972) and are observed in various conditions, including problem solving (Arellano and Schwab 1950; Ishihara and Yoshii 1972), continuous arithmetic operations (Ishihara and Yoshii 1972; Sasaki et al. 1994, 1996c), verbal and spatial tasks (Gevins et al. 1979), working memory tasks of verbal and spatial modalities (Gevins et al. 1997; Grunwald et al. 1999; McEvoy et al. 2001; Smith et al. 1999), Stroop tasks (Yamada 1998), video game operation (Laukka et al. 1995; Slobounov et al. 2000; Smith et al. 1999; Yamada 1998), time measuring tasks (Sasaki et al. 1996b), meditation (Aftanas and Golochekkin...
2001; Sasaki et al. 1996a), error-monitoring (Luu et al. 2001, 2003, 2004), and the peek-a-boo game of infants (Stroganova et al. 1998). Individual differences in the appearance of Fm theta activity have been reported. Subjects with higher Fm theta activity tend to be less anxious, less neurotic, and more extrovert (Mizuki et al. 1984), and have higher cognitive ability (Gevins and Smith 2000). Higher Fm theta activity in patients with major depression predicts a better response to treatment (Pizzagalli et al. 2001). These findings suggest that Fm theta oscillations may play an important role in attentional functions.

However, the physiological basis of Fm theta oscillations is still unclear. Since invasive study in the human subject is allowed only in limited cases, it would be rather difficult to investigate their neural substrate and functional mechanisms in the human brain. If a monkey model for Fm theta oscillations was available, it would be possible to take advantage of many techniques, e.g. single cell recording, ablation, electrical stimulation, and pharmacological methods. Consequently, we developed a monkey model as follows: Human Fm theta oscillations have been observed mostly in tasks requiring intellectual ability, which are too difficult for the monkey. As a substitute, we chose a self-initiated hand movement task with a waiting period. The
task required the monkey to wait for a fixed interval after movement before carrying out the next movement. This would require the monkey brain to be loaded with the executive attention (Posner and Rothbart 1998) of self-control, internal timing, readiness for action, and assessment of result, successively in the course of task execution. We examined the feasibility of the model by recording the cortical field potentials and showed that this task successfully induced theta oscillations in the frontal cortex. We identified the source of the currents that generated the oscillatory field potentials in the theta frequency range using electrodes arranged in pairs, one at the surface and one deeper in the cortex, and confirmed that the theta activity recorded was not a product of volume conduction from a remote source. Recording from the mesial wall of the hemisphere and the inside of the sulci, as well as the dorsolateral convexity of the brain, we investigated the nature of the theta activity, including the source distribution, frequency, task-related power modulation, inter-cortical correlations, and phase relations to the task. The homology to human Fm theta oscillations was then evaluated.

MATERIALS AND METHODS
Subjects

Three adult Japanese monkeys (4-6 kg, 2 female and 1 male) were used in the study, as approved by the institutional ethics committee. All experimental procedures were carried out in accordance with the NIH/ILAR Guide for the Care and Use of Laboratory Animals.

Behavioral task

During the experiment, the monkeys were seated in a primate chair equipped with a hand lever, a reward dispenser, and a head holder (Fig. 1A). From 24h before each experimental day, the water supply was restricted to half the amount of their average daily free drink. The task was to lift a lever with the hand in the monkey’s own time without external cues. When the monkey kept holding the lever in the resting position for more than a fixed waiting period before lifting the lever, the movement was rewarded with a drop of water (0.2 ml approx., delivered 0.6 s after the onset of movement). The holding of the lever by the monkey was monitored by an electrostatic touch sensor. If the monkey released the lever or made a premature movement, it initialized the timer for the waiting period. Starting from 2 s, the waiting period was
gradually increased in the early training phase. As the waiting period increased, the task was considered to be more difficult. The waiting period was finally set to 6 s, and the monkeys were trained for several weeks after they had reached a steady state. This waiting period was determined so that the monkeys succeeded in about two thirds of the trials.

**Recordings**

Electrodes were chronically implanted under pentobarbital sodium anesthesia (initial dose more than 35 mg/kg iv, followed by additional injections as needed). The electrodes for recording cortical field potentials (silver needles of 0.20 mm diameter, insulated by Teflon except at their pointed tip) were arranged in pairs, with one of each pair at the surface and the other at a depth of 2.5 – 3.5 mm at various cortical sites (Fig. 1B), and were fixed to the skull with acrylic resin and screws. Electrodes for the electrooculogram (EOG) were buried in the orbital bone and control electrodes were set in the bone marrow behind the ear on both sides. The linked control electrodes served as the reference for the cortical field potentials. After more than a month of recovery period, re-training and recording sessions were initiated. Data were
recorded in the task and resting (Rest) conditions. In the latter, the monkey was awake and seated, but not engaged in any particular task. The cortical field potentials and EOGs were processed by amplifiers at a 5 s time constant and with a 100 Hz high cut filter, digitized at 250 Hz, and stored in a computer.

**Data analysis**

The main origin of the cortical field potential is synaptic activity on the apical dendrites of pyramidal neurons (Fig. 2Aa) (for review, see Mitzdorf 1985). When populations of apical dendrites in a cortical region are synchronously activated at approximately the same location along their length, the contribution from the synaptic activity can overlap and produce a measurable electric potential gradient along the surface-depth direction within the cortex (Fig. 2Ab). The paired surface (S) and depth (D) electrodes were arranged to measure the dipole component of such an electric field (Fig. 2B). If oscillatory field potentials are generated between the S and D electrodes, the S and D potentials are recorded in opposite polarities and the phase difference should be around pi (Fig. 2Ba). Conversely, in a situation where the field potentials originate from a remote source, the S and D signals probably have a common polarity.
and the phase difference should be around zero (Fig. 2Bb). Therefore, by calculating the surface minus depth (S–D) potential, we are able to reduce the signal components of remote origins. This analysis has already been established as a useful method for assessing the source localization (e.g. Hashimoto et al. 1981; Sasaki et al. 1981, 1982). In this study, we used S–D potentials to evaluate regional activity, and examined the phase difference between S and D to assess whether a signal component found in the S–D potentials was generated at the recording site.

The data from the task condition were segmented into overlapping artifact-free epochs of 1024 ms (256 points) giving a resolution of 0.98 Hz using Discrete Fourier Transform (DFT). The data from Rest were consecutively segmented into non-overlapping artifact-free epochs of 1024 ms. The epoch data were processed by the removal of DC bias and linear trend, application of a window function (a Kaiser window with the adjustable parameter set to 4 π), and DFT. To calculate event-related spectra at a specified latency, denoted by \( t \), from the onset of an event (movement), the operation was carried out on the set of epochs whose centers were \( T(n) + t \) \( (n = 1, 2,..., N) \), where \( n \) is the trial number, \( N \) is the total trial number, and \( T(n) \) is the onset time of an event in \( n \)th trial (Fig. 2DE). The transition of spectra was obtained by moving \( t \)
in 0.1 s steps. To stabilize the variance, we applied a logarithmic transformation to the power spectra before calculating the mean and other statistical values (Halliday et al. 1995). Exponential transformation was applied to return the data to the original space before displaying the power spectra.

In order to analyze phase-locking between oscillations and external events (movement and reward), we calculated the phase relative to epoch for S–D potentials (Fig. 2 C). Phase relative to epoch is defined as the angle \( \phi \), where the complex number of the DFT product at a specified frequency is expressed in the polar coordinate form of \( Ae^{i\phi} \). The null hypothesis of uniformity for the distribution of \( \phi \) was tested using the Rayleigh statistic,

\[
R = \frac{\sqrt{\left(\sum \cos \phi \right)^2 + \left(\sum \sin \phi \right)^2}}{N}.
\]

The summation in the above expression covered the set of epochs whose centers were \( T(n) + t \ (n = 1, 2, \ldots, N) \) (Fig. 2 D). The value of \( R \) ranges from 0 to 1, and \( R = 1 \) indicates complete phase locking. To examine phase-locking between two potentials \( X \) and \( Y \), we calculated the Rayleigh statistic \( R \) for the phase difference \( \phi = \phi_X - \phi_Y \), where \( \phi_X \) and \( \phi_Y \) are the phase relative to epoch of the two potentials (Fig. 2 E).

When we needed to confirm that an elevation in the coherence or Rayleigh statistic
between two potentials, X and Y, was a true effect and not caused by a systematic error hidden in the experimental arrangement, we calculated the control statistic between the unmatched pairs of shuffled data, \( X(1) - Y(2), X(2) - Y(3), X(3) - Y(4), \ldots, X(N-1) - Y(N) \), and \( X(N) - Y(1) \), where \( X(n) \) and \( Y(n) \) stand for the potentials X and Y in the \( n \)th trial and \( N \) is the total trial number. These statistical values were compared with the 95% confidence limits which were theoretically computed (Halliday et al. 1995).

**Recording sites**

After electrophysiological investigations, the monkeys were deeply anesthetized with an overdose of pentobarbital sodium and were perfused through the heart with 10% formaldehyde neutral buffer solution. The brains were cut into 50 \( \mu \)m-thick sections and stained for Nissl bodies. The penetration of recording electrodes was identified and photographed using a microscope. After confirming that degenerative tissue changes did not extend beyond the region adjacent to the electrodes, the recording sites were plotted on a standard brain map showing the positions in relation to the morphological landmarks of the major sulci and corpus callosum. The map was adopted from the Stereotaxic atlas of the brain of Macaca fuscata (Kusama and
Mabuchi 1970) and was complemented with a mesial view of our own brain specimen of similar dimensions. The cortical subdivisions were drawn at the estimated positions consulting previous studies (Ongur and Price 2000).

RESULTS

Modulation of theta oscillations

We noted characteristic theta oscillations in particular cortical regions (e.g. anterior cingulate cortex; Fig. 1 C-E) in all three monkeys. Figure 3 shows a representative record of 686 trials in Monkey A. In Fig. 3A, a segment of the raw data is shown with a timing chart of the task. The traces S and D are the raw cortical field potentials recorded at the surface and at a 3 mm depth in Walker’s area 9 ipsilateral to the moving hand (i.e. left in this case). Sinusoidal waves at about 5 Hz often appeared in the raw traces in opposite polarities between S and D. Part of the data are expanded in the inset. With waxing and waning, the amplitude of the theta waves sometimes measured up to about 200 μV (peak to peak) in the S–D trace.

The behavioral performance is shown as a histogram of the onset of the preceding and the following movements (Fig. 3B). 195 out of 686 trials were unrewarded because
the monkey had not held the lever for a sufficient duration during the waiting period (Fig. 3B red). The remaining 491 of 686 trials were rewarded (Fig. 3B black).

A time-frequency analysis showed that the theta power of the S–D potential in area 9 was modulated in relation to the task (Fig. 3C). The power in the theta band is plotted in Fig. 3D. It was gradually increased from a few seconds before the movement and reached a peak immediately after the movement in both the rewarded and unrewarded trials. In the rewarded trials, it reached a second peak after the reward delivery, while it rapidly decreased in the unrewarded trials. The modulation was noted throughout the whole theta band, and was most prominent at 4.9 Hz in this monkey.

Coherence and phase

The coherence between S and D in the theta band was significant at the 95% confidence level throughout the trials, for both the rewarded and the unrewarded cases (the solid and broken lines in Fig. 3E). Control coherence was calculated between the unmatched pairs of $S(1)$-$D(2)$, $S(2)$-$D(3)$, $S(3)$-$D(4)$, ..., $S(N-1)$-$D(N)$, and $S(N)$-$D(1)$, where $S(n)$ and $D(n)$ stand for the S and D potentials in the $n$th trial and $N$ is the total
trial number. The control coherence (the dotted lines in the lower part of Fig. 3E) was not significant at the 95% confidence level, and showed no clear event-related modulation. This indicates that the significant coherence between the matched pairs (the solid and broken lines in Fig. 3E) cannot be attributed to a systematic error hidden in the recording arrangement.

The phase angle of S as referenced by D was $0.97\pi \pm 0.03\pi$ (mean±SD at 3.9 Hz), $0.97\pi \pm 0.02\pi$ (4.9 Hz, plotted in Fig. 3F), $0.98\pi \pm 0.01\pi$ (5.9 Hz), and $0.99\pi \pm 0.01\pi$ (6.9 Hz) during the time region $[-10\ s, 10\ s]$.

This theta activity was probably generated from the cortical region between the S and D electrodes and was not a result of a current spread from remote sources, because the phase angle between S and D was around $\pi$ (Fig. 3F and Fig. 2D).

Statistical evaluation

For quantitative and statistical evaluation of changes in spectra, the time regions of interest, $R1=[-3.7\ s, -2.8\ s]$, $R2=[-2.0\ s, -1.1\ s]$, $R3=[-0.3\ s, 0.6\ s]$, and $R4=[1.2\ s, 2.1\ s]$, were set as marked in Fig. 3D. R1, R2, and R3 were arranged to analyze the gradual increase in the theta power from the pre-movement base to the
post-movement peak. R4 was adjusted to compare the difference between the rewarded and unrewarded trials. In Fig. 3G, the mean power spectra are calculated for each time region and Rest. Rest included 620 epochs. It indicates that the modulation of power spectra was maximal in the same theta frequency in both the pre-movement increase and the transient rise after reward.

For statistical evaluation of the gradual increase in the theta power, the theta power in each of R1, R2, and R3 was calculated on a per trial basis for the rewarded trials, collecting the epochs whose center was included in the respective time regions (Fig. 2D), and compared by one tailed paired Student’s t-test. The increase in the theta power at 4.9 Hz was statistically significant for both the comparison between R1 and R2 ($t=7.47, p < 2e^{-13}$) and between R2 and R3 ($t=8.27, p < 7e^{-16}$).

For statistical assessment of the difference in theta power between the rewarded and unrewarded trials, the theta power in R4 was calculated on a per trial basis, and compared using two tailed two sample Welch’s t-test. The difference was statistically significant ($t=11.6, df=483, p < 9e^{-28}$).

The theta power in Rest was lower than in the task condition (Fig. 3G), and was compared with the theta power in R1 calculated on a per trial basis for the rewarded
trials using two tailed two sample Welch’s t-test. The difference was statistically significant ($t=7.86$, $df=1061$, $p < 9e^{-15}$).

*Other examples and population results*

The same kind of modulation of theta oscillations was observed in several recording sites in areas 9 and 32 of the three monkeys. Representative data recorded from Monkey B and Monkey G are presented in Fig. 4ABCD. The same time regions of interest for Monkey A were set for Monkey B and G for further analysis (Fig. 4C and D). The modulation was also recognizable in the grand mean power spectra in these areas (Fig. 4EF). When all the power spectra obtained from the recording sites in area 32 were averaged across the monkeys, the resulting grand mean spectra showed essentially the same modulation in the theta band as in Fig. 3G (Fig. 4E). This was also the case for area 9 (Fig. 4F). These results indicate that theta modulation may be a common feature of these areas.

*Cortical distribution*

To determine the cortical distribution of such theta activity, both types of theta
power modulation, i.e. the gradual increase preceding the movement and the
difference between the rewarded and unrewarded trials, were statistically tested in all
three monkeys across all of the recording sites. The analysis was based on the records
of 491+195, 545+196, and 555+285 (rewarded+unrewarded) trials, each taken in a day,
for Monkey A, B, and G, respectively. It was carried out at the frequency with the peak
power in the theta band for the individual monkeys (4.9 Hz for Monkey A; 5.9 Hz for
Monkey B and G; see Fig. 6).

The gradual increase in theta activity was determined by the following criteria:
Criterion 1, the power in R2 was significantly higher than in R1 (one tailed paired
Student’s t-test; \(p < 0.05\)); Criterion 2, the power in R3 was significantly higher than in
R2 (one tailed paired Student’s t-test; \(p < 0.05\)); Criterion 3, the coherence between S
and D was significant (\(p < 0.05\)) and the phase angle between S and D potentials was
in antiphase within the range \([0.5\pi, 1.5\pi]\) in more than half of the epochs in both R2
and R3. The theta power increase was regarded as significant only when all three
criteria were met.

The difference in theta power between the rewarded and unrewarded trials was
assessed by the following criteria: Criterion A, the theta power in R4 in the rewarded
trials was significantly higher than in the unrewarded trials (two tailed two sample Welch’s t-test, \( p < 0.05 \)); Criterion B, the coherence between S and D was significant (\( p < 0.05 \)) and the phase angle between S and D potentials was in antiphase within the range \([0.5\pi, 1.5\pi]\) in more than half of the epochs in R4 in the rewarded trials; Criterion C, the power modulation was observed mainly in the theta band (4-7 Hz).

The cumulative result is plotted in Fig. 5. Eleven recording sites out of the total 99 sites were determined as significant generators of the gradual increase; 8 of 11 were found in Walker’s area 9 and the remaining 3 were in area 32. These corresponded to 50% of the total 16 sites in area 9 and 75% of the total 4 sites in area 32. There was no significant theta increase in areas 24, 46, 12, 8B, 6, 7, the primary motor area (MI), or the primary somatosensory area (SI). As for the difference between the rewarded and unrewarded trials, 12 sites were determined as significant sites (7 in area 9, 4 in area 32, and 1 in area 24). These mostly overlapped with the significant sites for the gradual increase. The spectra are plotted in Fig. 6 and the scores for the criteria for all the significant theta generators and some of the surrounding sites are given in supplemental materials, Tables S1 and S2. The significant theta generators showed essentially the same spectral modulation in the theta band as in Fig 3G. Figure 6
shows that both the theta modulations preceding the movement and after the reward were very similar in their frequency and cortical distribution.

Some sites in the dorsal part of area 46 (46d) showed monotonic increase of the theta power through the time regions of R1, R2, and R3. However, theta oscillations in these sites were in-phase between the S and D. They passed Criteria 1 and 2, but were rejected by Criterion 3 (e.g. Fig. 6 and supplemental materials, Table S1, Monkey A-b and e). This theta activity may be caused by current spread from remote sources in areas 9 and/or 32 (Fig. 2Bb). Some sites in area 46 passed Criteria A and B, but showed a power modulation in a broader frequency range than the theta band (e.g. Fig. 6 and supplemental materials, Table S2, Monkey A-f, Monkey G-i). These were rejected by Criterion C. In area 46d, the power in the alpha and beta bands (approx. 8-30 Hz) often increased through the time regions of R1, R2, and R3, and was higher in the rewarded trials than in the unrewarded trials in the time region of R4 (e.g. Fig. 6. Monkey A-b and e, Monkey B-i, and Monkey G-b and i). These results indicate that the oscillatory activity in area 46 has a different profile from that in areas 9 and 32.

When we simply repeat the statistical test across multiple recording sites, some sites may be falsely judged as significant generators by chance. To overcome this
problem of multiple comparisons, we applied the same analysis to data taken on different days. This second analysis was based on the records of 378+230, 558+160, and 459+155 (rewarded+unrewarded) trials for Monkey A, B, and G, respectively. All the significant theta generators in Fig. 5 were again identified as significant generators except for one. The exception was the site in area 24 (Monkey G-f in Fig. 6) in which Criterion A was not met ($t=0.81, df=213, p>0.4$), therefore the theta generator in area 24 was not confirmed. The significant theta generators in areas 9 and 32 were confirmed not to be false positive by chance.

To ensure that the changes in theta power were not contaminated by EOG, we examined the power spectra of EOG and found no corresponding activity in the theta band.

Task condition vs. Rest

As shown in Fig. 4EF and Fig. 6, there was a tendency that the theta power in Rest was lower than in the task condition. The difference in the theta power was statistically tested by two tailed two sample Welch’s $t$-test across all the significant theta generators identified in the above analysis (8 sites in area 9 and 4 in area 32).
The analysis was carried out at the frequency of the peak in the theta band for individual monkeys and based on 620, 747, and 612 epochs in Rest and 491+195, 545+196, and 555+285 (rewarded+unrewarded) trials in the task condition for Monkey A, B, and G, respectively. The power in the task condition was calculated on a per trial basis.

For all the significant theta generators, the difference between Rest and R1 in the rewarded trials was statistically significant ($p < 0.05$).

As for the difference between Rest and R4 in the unrewarded trials, it was statistically significant ($p < 0.05$) in 6 sites (4 in area 9 and 2 in area 32; Monkey A·a and d, Monkey G·d, e, g, and h in Fig. 6), but not significant in the remaining 6 sites (4 in area 9 and 2 in area 32; Monkey B·a, f, g, i, and j and Monkey G·a in Fig. 6). In the cases where there was a significant difference, the theta power was lower in Rest than in R4 in the unrewarded trials.

The results indicate that the theta power in Rest was lower than in the pre-movement period and that the theta power in R4 in the unrewarded trials sometimes decreased nearly to the level in Rest.
Inter-cortical coupling

Theta oscillations in area 32 and area 9 in both hemispheres showed marked inter-cortical coupling (Fig. 7). Coherence was maximal at the theta frequency between these areas as shown in the contour plots (Fig. 7B). Coherence and the Rayleigh statistic \( R \) between these areas were significantly high at the theta frequency throughout the trial (Fig. 7C). The phase angles were generally in phase within the range \([-0.5\pi, 0.5\pi]\), and almost constant throughout the trial (Fig. 7C). The relative phase in the ipsilateral area 9 as referenced by the contralateral area 9 was \( 0.02\pi \pm 0.01\pi \) (mean \( \pm \) SD) during the time region \([-10 s, 10 s]\) in Monkey A, \(-0.09\pi \pm 0.01\pi \) in Monkey B, and \(-0.05\pi \pm 0.01\pi \) in Monkey G. The relative phase in area 32 as referenced by area 9 in the same hemisphere was \(-0.04\pi \pm 0.02\pi \) in Monkey B and \(-0.28\pi \pm 0.02\pi \) in Monkey G. Since the control coherence and \( R \) (dotted lines in Fig. 7) calculated between the unmatched pairs of potentials were not significant at the 95% confidence level, the significant coherence and \( R \) between the matched pairs cannot be attributed to a systematic error contained in the recording arrangement. The results indicate that theta oscillations in areas 9 and 32 are significantly correlated and synchronized.
Latency of peak theta power

The latency of peak theta power was measured across the significant theta generators identified above. The latency of the first peak after the movement onset was $0.5 \pm 0$ s (mean±SD, n=2) for Monkey A, $0.6 \pm 0.05$ s (n=4) for Monkey B, and $0.4 \pm 0.1$ s (n=5) for Monkey G. The latency of the second peak after the reward delivery was $0.7 \pm 0$ s (n=2) for Monkey A, $0.8 \pm 0.04$ s (n=5) for Monkey B, and $1.1 \pm 0.1$ s (n=5) for Monkey G. The analysis was based on 491, 545, and 555 rewarded trials for Monkey A, B, and G, respectively.

Phase relations between theta oscillations and external events

Phase-locking of the theta activity to the external events (movement onset and reward delivery) was assessed by the Rayleigh statistic $R$. Although $R$ transiently rose above the 95% confidence limit (with the Bonferroni correction for multiple comparisons) at the moments of the movement and the reward delivery (Fig. 8), the rise was noted in a relatively broader frequency band (approx. 1-20Hz; data not shown). In other time regions, $R$ was not significantly elevated throughout the
analyzed frequencies (1-125 Hz). The results indicate that the phase of the pre-movement theta oscillations is not locked to the movement onset and the phase of the post-reward theta oscillations is not locked to the reward delivery.

DISCUSSION

The main findings of the present study are as follows: The sources of the current generating the oscillatory field potentials in the theta frequency range were identified in areas 9 and 32 while the monkeys performed the self-initiated hand movement task. The frequency of the peak power in the theta band was 4.9 Hz for Monkey A and 5.9 Hz for Monkey B and G. We noted two phases of theta modulation in relation to the task, i.e. the pre-movement gradual increase and the transient increase after reward. In Rest, the theta power was lower than in the pre-movement periods. In the unrewarded trials, the second increase did not occur, and the theta power sometimes decreased nearly to the level in Rest. Significant inter-cortical correlation in the theta band was found between areas 9 and 32. No significant phase-locking was found between the external events (movement and reward delivery) and theta oscillations preceding the movement and those after the reward.
Homology with human Fm theta oscillations

A monkey model for human Fm theta oscillations was developed and its validity has been tested in the present study. We propose that this model is likely to represent the monkey counterpart of human Fm theta oscillations and would be useful for studying executive functions in the frontal cortex for the following three major reasons: First, the source distribution identified in the model is compatible with that of human Fm theta oscillations (Source distribution). The second is the correspondence in the frequency (Frequency of oscillations). The third and last reason is that the present theta activity in the monkey is generated in a manner strongly dependent on attentional processes, similar to human Fm theta oscillations (Dependence on attentional processes). We give a more detailed explanation for these reasons below.

(1) Source distribution. There has been no report of direct recordings that locate the source regions of human Fm theta oscillations. According to non-invasive studies by EEG and magnetoencephalogram (MEG), they have been estimated as being around the anterior cingulate cortex (ACC), the mesial frontal cortex, and/or the dorsolateral frontal cortex (Asada et al. 1999; Gevins et al. 1997; Ishii et al. 1999;
Pizzagalli et al. 2001; Sasaki et al. 1994). As areas 9 and 32 are among these regions, we can consider the cortical distribution of the present theta oscillations to be compatible with that of human Fm theta oscillations.

(2) **Frequency of oscillation.** The peak power of human Fm theta oscillations has been reported at about 5-7 Hz (Asada et al. 1999; Gevins et al. 1997; Inouye et al. 1988; Iramina et al. 1996; McEvoy et al. 2001; Sasaki et al. 1996a,c; Slobounov et al. 2000; Smith et al. 1999; Yamada 1998). The present theta frequency (4.9 Hz for Monkey A and 5.9 Hz for Monkey B and G) shows a good correspondence with that of human Fm theta oscillations.

(3) **Dependence on attentional processes.** The dependence on attentional processes is one of the significant characteristics of human Fm theta oscillations. Although human Fm theta oscillations are observed in apparently diverse circumstances (see Introduction), it has been established that they are involved in common neural processes for attentional functions (Inanaga 1998; Ishihara and Yoshii 1972). In the present experiment, we observed two phases of theta modulation in areas 9 and 32, i.e. a gradual increase in theta power preceding the movement and a transient rise in response to the reward. As no direct cues for timing were given in the task, the
monkey had to time the duration internally, and had to modify the internal guess criterion retrospectively, depending on whether the reward was acquired successfully or not. The first phase of gradual increase may be related to self-control, internal timing, and readiness for action. The second phase of transient rise may be involved in the assessment of reward. This reward-related theta modulation may also be associated with the process of success/error judgment (Falkenstein et al. 1991; Gehring et al. 1993; Gemba et al. 1986; Luu et al. 2003). According to Posner et al. (1994, 1998), it seems that ‘executive attention’ is actively involved in the present experimental paradigm, which requires a sequential occurrence of self-control, internal timing, readiness for action, assessment of reward, and success/error judgment. Therefore, it is most likely that the task in the present study loaded the monkey with executive attention or attention processes in general, and that the theta activity was associated with the attentional load of the task. Compatible with such requirement of attention, the theta activity during the pre-movement periods in the task condition was significantly higher than in the resting condition (Rest) in the present experiments. Although we should investigate this interpretation further, these findings suggest that the theta oscillations identified in the present study are
associated with attentional processes, similar to human Fm theta oscillations. Theta oscillations dependent on attentional processes can also be observed in a task in which hand movement is triggered by warning and imperative stimuli: the theta power in areas 9 and 32 was higher in the warning-imperative interval than in the pre-warning period (Tsujimoto et al. 2003).

On these grounds, we propose that the theta oscillations identified in areas 9 and 32 may serve as a relevant model for human Fm theta oscillations.

*Functional localization and theta oscillations*

Several lines of evidence indicate that, in both the monkey and the human, the ACC is involved in executive processes, including attention allocation, motivated attention, assessment of motivational content, drive, emotion, error detection, motor control, and cognition (for review, see Carter et al. 1999; Ingvar 1994; MacLeod and MacDonald 2000; Mesulam 1981; Paus 2001; Posner et al. 1988, 1990, 1998; Vogt et al. 1992). It is also accepted that the ACC is functionally not a homogeneous area. Activation of area 32 is more often associated with difficult tasks than area 24 (Paus et al. 1998). As a relative tendency, the rostral ACC is involved in affective functions,
while the caudal ACC is related to cognitive functions (for review, see Bush et al. 2000; Devinsky et al. 1995; Drevets and Raichle 1998; Paus 2001). The behavior of the theta oscillations found in the present study is in accordance with such functional localization in the rostral ACC and area 32. Two topics which have been independently studied in the human, i.e. the executive function of the rostral ACC, as revealed mainly by functional neuroimaging and neuropsychology, and Fm theta oscillations, as investigated by EEG and MEG, may be two facets of the same phenomenon.

Theta oscillations in Walker’s area 9 are another important finding. The functional role of area 9 is still under debate, although its involvement in executive monitoring within working memory has been suggested by a lesion study (Petrides 2000). The present results suggest that area 9 may be involved in attentional processes in cooperation with the rostral ACC. The coherence and synchronization of theta oscillations between areas 9 and 32 revealed by the present study suggest close functional coupling of these areas. Anatomically, area 9 of the monkey is situated in a pivotal position to interface with both the ACC and the dorsolateral frontal cortex, such as Walker’s area 46 and the premotor area, interconnecting them through reciprocal cortico-cortical projections (Barbas et al. 1999; Carmichael and Price 1996;
Morris et al. 1999; Passingham et al. 2002). There is supportive evidence by positron emission tomography for the involvement of areas 9 and 32 in executive functions: in both areas 9 and 32, the regional cerebral blood flow is correlated to the supposed willingness of the monkey to the task (Tsujimoto et al. 2000).

**Interaction with other activities**

If theta oscillations interact with external events such as movement or reward delivery, there may be phase-locking between the theta oscillations and the external events. The rise of the Rayleigh statistic $R$ was, however, noted only at the moments of the movement and reward delivery (Fig. 8), and was not limited to the theta band. In time-domain, it probably corresponds to transient evoked potentials following the movement and reward delivery. As for the theta oscillations during the pre-movement gradual increase and the transient rise after reward, we obtained negative evidence for phase-locking. This does not necessarily mean that the oscillatory phase is not important or that there is no interaction. Since the interaction between external events and areas 9 and 32 is presumably not direct but mediated by other regions in the brain, the phase relations may be blurred during such polysynaptic relays.
The present results pose a question as to how the theta rhythms in areas 9 and 32 are generated and interact with other activities in the brain. The common anatomical features of areas 9 and 32 are the connections with the thalamic dorsomedial (MD) and ventral anterior (VA) nuclei, caudate nucleus, hypothalamus, and hippocampal/parahippocampal regions (Barbas et al. 1991, 1995; Goldman-Rakic and Porrino 1985; Morris et al. 1999; Ray and Price 1993; Rempel-Clower and Barbas 1998; Yeterian and Pandya 1991). There may be an interaction between these structures and areas 9 and 32 through theta oscillations.

The hippocampus may be particularly important in this context. It is thought that theta oscillations in the hippocampus and their interaction with the neocortex have essential roles in the neural system (for review, see Buzsaki 2002; Vanderwolf 1988; Vertes and Kocsis 1997; Vinogradova 1995). In rodents, the activity of the prefrontal neurons is correlated with and phase-locked to hippocampal theta oscillations (Hyman et al. 2005; Siapas et al. 2005). In monkeys, a well-practiced self-initiated hand movement is preceded and accompanied by desynchronization of low-frequency rhythmic potentials in the hippocampus, suggesting that the hippocampus may also be involved in the initiation and control of voluntary movement in the primate (Arezzo et
al. 1987). The prefrontal-hippocampal interaction should be investigated further.

Conclusion

We have developed a monkey model for human Fm theta oscillations. A homologue of human Fm theta oscillations was identified in areas 9 and 32. The findings suggested that theta oscillations in areas 9 and 32 may play an important role in attentional processes. The model may be useful for studying executive functions of the frontal cortex.
ACKNOWLEDGMENTS

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DISCLOSURES

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REFERENCES


Barbas H, Ghashghaei H, Dombrowski SM, and Rempel-Clower NL. Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *J Comp*


Goldman-Rakic PS and Porrino LJ. The primate mediodorsal (MD) nucleus and its


**Hyman JM, Zilli EA, Paley AM, and Hasselmo ME.** Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. *Hippocampus* 15: 739-749, 2005.


**Ingvar DH.** The will of the brain: cerebral correlates of willful acts. *J Theor Biol* 171:
7-12, 1994.


Sasaki K, Tsujimoto T, Nambu A, Matsuzaki R, and Kyuhou S. Dynamic activities of


**Tsujimoto T, Ogawa M, Tsukada H, Kakiuchi T, and Sasaki K.** Decline of the monkey's


FIGURE LEGENDS

FIG. 1. A: The monkey was engaged in a self-initiated hand movement task. B Schematic examples of the surface (S) and depth (D) electrodes placed in the frontal section of the brain. The electrodes were arranged to form S and D pairs. (a) In the cingulate cortex, they were placed from a medial approach. (b) Three electrodes formed two pairs (S1·D and S2·D), at the medial corner of area 9. (c) A simple pair was used on the dorsolateral aspect of the cortex. (d) Five electrodes formed four pairs (S1·D1, S3·D1, S3·D2, and S2·D2), at the sulcus. C Mesial view of the brain showing the recording sites in the anterior cingulate cortex in Monkey G. Circles indicate the penetration of electrodes. Shallow grooves where the electrode leads passed through can be seen on the cortical surface (four arrows). D Nissl-stained section (50 μm thick) taken at the broken line in C. The arrow indicates a trace of a depth electrode (Monkey G·e in Fig. 6). E The rectangular region in D is expanded to show the cortical structure. Note that the degenerative change is recognizable only in the tissue adjacent to the trace. Abbreviations: ACC (anterior cingulate cortex), CS (cingulate sulcus), PS (principal sulcus).
FIG. 2. Outline of data analyses. A: Generation of cortical field potentials. (a) Extracellular currents (arrows) caused by synaptic activity generate a field potential in the extracellular volume conductor. The figure is an example of cases in which excitatory synaptic input arrived at the distal portion of the apical dendrite of a pyramidal neuron. (b) When populations of pyramidal neurons are synchronously activated at the distal portion of the apical dendrite, the contribution from the synaptic activity can overlap and produce a measurable surface-negative and depth-positive electric field within the cortex. Alternatively, when the proximal portion of the apical dendrites is activated by excitatory synaptic input, a surface-positive and depth-negative field potential will be produced. B: Recording field potentials with S and D electrodes. (a) If oscillatory field potentials are generated at the location of the recording electrodes, they are recorded as antiphase signals by the S and D electrodes. As the S and D signals have opposite polarities, the amplitude of the signals becomes bigger in S–D potentials. (b) If field potentials originate from a remote source, they are probably recorded as in-phase signals by the S and D electrodes. The amplitude of such activities is canceled and reduced in S–D potentials, as the S and D signals have the same polarities. C: Phase relative to epoch indicates the relative location of
oscillatory activity within an epoch (see text). **D.** Time series data of S–D potentials were segmented into epochs with \( t \) moving in 0.1 s steps, and converted to Fourier series data by Discrete Fourier Transform (DFT). Power spectra and the Rayleigh statistic \( R \) for the phase relative to epoch were calculated at each step of \( t \) in an event-related manner. Power spectra per trial basis were used for statistical analyses (see text). **E.** Correlation between two potentials (X and Y) was assessed by coherence and phase spectra and the Rayleigh statistic \( R \) for the phase difference, which were calculated from the Fourier series data of X and Y in the same event-related manner as in **D.** X and Y can be the S and D potentials of the same recording site or two S–D potentials of different areas.

**FIG. 3.** Representative data of 686 trials recorded in Monkey A are shown. **A:** A segment of the raw waveform recorded from the surface (S) and the depth (D) electrodes in the left area 9 (Monkey A-a in Fig. 6) is shown with the time markers of lever movement and reward delivery. The S–D potential is the arithmetic difference between the S and D potentials. The scale of 200 microvolt is for S, D, and S–D potentials. The S and D potentials in the dotted rectangle of 1 s duration are expanded
in the upper part. B: The onset of the preceding and following movement is shown as a stacked histogram for the rewarded (n = 491) and unrewarded trials (n = 195) in 100 ms bins. The time axis zero is set to the onset of movement. C: The temporal change in the power spectra is calculated for the S–D potential, separately for the rewarded and the unrewarded cases. Power is displayed in normalized power per unit bandwidth, namely power spectral density. The color scale is for both of the contour plots. D: The time course of the power is plotted at 3.9, 4.9, 5.9, and 6.9 Hz, separately for the rewarded and the unrewarded cases. E: The time course of the coherence between S and D is plotted, separately for the rewarded and the unrewarded cases (solid and broken lines). The horizontal broken lines denote the theoretical 95% confidence limit for significant coherence for the rewarded (black) and the unrewarded (red) cases. The dotted lines in the lower part of the figure are the control coherence calculated from the unmatched pairs of data for the rewarded (black) and the unrewarded (red) cases (see text). The control coherence is calculated for 3.9, 4.9, 5.9, and 6.9 Hz, and is displayed without discriminating the frequencies. F: The phase angle of S as referenced by D is plotted at 4.9 Hz. The line width of the plot represents the 95% confidence limit. G: The mean power spectra are compared between R1, R2, R3, and
R4 time regions as indicated in D and Rest. For R1, R2, and R3, the spectra are of the rewarded cases. For R4, they are compared between the rewarded and the unrewarded cases. Rest included 620 epochs.

**FIG. 4.** Representative data recorded from Monkey B (A and C) and Monkey G (B and D) and the grand mean spectra (E and F). ABCD The task performance (A and B) and the time course of the theta power (C and D) are displayed in the same formats as in Fig. 3 B and D. Recording sites are Monkey B-a and f and Monkey G-a and d in Fig. 6. EF The grand mean power spectra in areas 32 and 9 were calculated across the monkeys. For area 32 (E), power spectra obtained from the total 4 recording sites (2 in Monkey B and 2 in Monkey G) were averaged. For area 9 (F), data from the total 16 sites (4 in Monkey A, 8 in Monkey B, and 4 in Monkey G) were combined (see Fig. 6 for their location). The mean power spectra in R1, R2, R3, and R4 were displayed as values relative to the mean power spectra in Rest. The analysis was based on the record of 620, 747, and 612 epochs in Rest and 491+195, 545+196, and 555+285 (rewarded+unrewarded) trials in the task condition for Monkey A, B, and G, respectively.
FIG. 5. Sites of significant theta modulation. The theta power changes were statistically tested for two properties: 1) the gradual increase preceding the hand movement and 2) the difference between the rewarded and unrewarded trials (see text). Black marks indicate the significant theta generators. The left part of the mark indicates whether the gradual increase in theta power was significant, and the right shows whether the theta power was significantly higher in the rewarded trials than in the unrewarded trials. Marks on the opened sulci represent the electrode pairs in the banks of sulci as shown in Fig. 1B (d) S3-D1 and S3-D2. Laterality is relative to the moving hand (ipsi and contra). Graphs show the numbers of the recording sites in which theta power change was significant or not significant. Abbreviations: SMA (supplementary motor area), CMAr (rostral cingulate motor area), MI (primary motor area), SI (primary somatosensory area).

FIG. 6. The mean power spectra are shown in the same format as in Fig. 3G for all the sites of significant theta modulation and for some of the surrounding sites. The spectra in the dotted rectangles (2.9–7.8 Hz) are expanded in the insets. The same marks as in
Fig. 5 are used. Spectra were obtained from the sites with the same alphabetical labels on the map. Laterality is relative to the moving hand (ipsi and contra).

**FIG. 7.** Inter-cortical coupling of theta oscillations. **A:** Coherence, phase, and the Rayleigh statistic \( R \) are calculated between the S–D potentials of areas 9 and 32 (Monkey A-a and d; Monkey B-a, f, and i; Monkey G-a, d, and g in Fig. 6). Arrows denote the direction of phase angle calculation which was arbitrarily defined: where an arrow is directed from \( Y \) to \( X \), the relative phase of \( X \) as referenced by \( Y \), \( \phi = \phi_x - \phi_y \), is calculated (see text). **B** The temporal change in the coherence spectra is calculated between the S–D potentials of two areas. The color scale is for all the contour plots. **C** Coherence, phase, and \( R \) are plotted at the frequency with the peak power in the theta band (4.9 Hz for Monkey A, 5.9 Hz for Monkey B and G). In the phase plot, three lines in the same color represent the estimate and the theoretical 95% confidence limit. The three lines are often so close that they are apparently fused together. The horizontal broken lines denote the theoretical 95% confidence limit for significant coherence and \( R \). The dotted lines are the control statistics calculated from the unmatched pairs of data (see text). The analysis was based on 491, 545, and 555 rewarded trials for
Monkey A, B, and G, respectively.

**FIG. 8.** Phase relations between theta oscillations and external events (movement and reward). The Rayleigh statistic $R$ is calculated for phase relative to epoch (see text). The horizontal broken lines denote the theoretical 95% confidence limits for significant phase locking; the upper lines are the limits with the Bonferroni correction for multiple comparisons across the time region $[-10\ s, 10\ s]$ and the lower lines are the uncorrected limits for each latency. The analysis was based on 491, 545, and 555 rewarded trials for Monkey A, B, and G, respectively. The recording sites are the same as in Fig. 7 (Monkey A·a and d; Monkey B·a, f, and i; Monkey G·a, d, and g in Fig. 6).
**TABLE S1** (supplemental online materials)

Pre-movement gradual increase assessed by Criteria 1, 2, and 3

<table>
<thead>
<tr>
<th>Recording site</th>
<th>Cr1</th>
<th>Cr2</th>
<th>Cr3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-a (area 9)*</td>
<td>$t=7.47, p&lt;2e^{-13}$</td>
<td>$t=8.27, p&lt;7e^{-16}$</td>
<td>1.0, 1.0</td>
</tr>
<tr>
<td>A-b (area 46d)</td>
<td>$t=5.99, p&lt;3e^{-9}$</td>
<td>$t=6.85, p&lt;2e^{-11}$</td>
<td>0.0, 0.4</td>
</tr>
<tr>
<td>A-c (area 46v)</td>
<td>$t=-4.01, p&gt;0.9$</td>
<td>$t=-0.33, p&gt;0.6$</td>
<td>1.0, 0.3</td>
</tr>
<tr>
<td>A-d (area 9)*</td>
<td>$t=8.11, p&lt;3e^{-15}$</td>
<td>$t=7.28, p&lt;7e^{-13}$</td>
<td>0.9, 0.6</td>
</tr>
<tr>
<td>A-e (area 46d)</td>
<td>$t=4.52, p&lt;4e^{-6}$</td>
<td>$t=3.83, p&lt;8e^{-5}$</td>
<td>0.0, 0.0</td>
</tr>
<tr>
<td>A-f (area 46v)</td>
<td>$t=-4.17, p&gt;0.9$</td>
<td>$t=0.15, p&gt;0.4$</td>
<td>1.0, 1.0</td>
</tr>
<tr>
<td>B-a (area 9)*</td>
<td>$t=2.75, p&lt;4e^{-3}$</td>
<td>$t=7.04, p&lt;3e^{-12}$</td>
<td>0.7, 0.7</td>
</tr>
<tr>
<td>B-b (area 9)</td>
<td>$t=0.10, p&gt;0.4$</td>
<td>$t=2.74, p&lt;4e^{-3}$</td>
<td>0.0, 0.0</td>
</tr>
<tr>
<td>B-c (area 9)</td>
<td>$t=7.11, p&lt;2e^{-12}$</td>
<td>$t=2.45, p&lt;8e^{-3}$</td>
<td>0.0, 0.0</td>
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<tr>
<td>B-d (area 9)</td>
<td>$t=5.55, p&lt;3e^{-8}$</td>
<td>$t=1.34, p&gt;0.05$</td>
<td>0.0, 0.0</td>
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<tr>
<td>B-e (area 9)</td>
<td>$t=0.88, p&gt;0.1$</td>
<td>$t=-0.14, p&gt;0.5$</td>
<td>0.0, 0.0</td>
</tr>
<tr>
<td>B-f (area 32)*</td>
<td>$t=2.94, p&lt;2e^{-3}$</td>
<td>$t=8.53, p&lt;8e^{-17}$</td>
<td>0.7, 1.0</td>
</tr>
<tr>
<td>B-g (area 32)</td>
<td>$t=0.03, p&gt;0.4$</td>
<td>$t=3.56, p&lt;3e^{-4}$</td>
<td>0.7, 1.0</td>
</tr>
<tr>
<td>Region</td>
<td>Area</td>
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<td>p-value</td>
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</tr>
<tr>
<td>B·h</td>
<td>24</td>
<td>1.21</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>B·i</td>
<td>9*</td>
<td>2.92</td>
<td>&lt;2e-3</td>
</tr>
<tr>
<td>B·j</td>
<td>9*</td>
<td>3.33</td>
<td>&lt;5e-4</td>
</tr>
<tr>
<td>B·k</td>
<td>6aβ</td>
<td>-2.42</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>B·l</td>
<td>46d</td>
<td>-0.37</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>B·m</td>
<td>46v</td>
<td>-1.12</td>
<td>&gt;0.8</td>
</tr>
<tr>
<td>G·a</td>
<td>9*</td>
<td>4.97</td>
<td>&lt;5e-7</td>
</tr>
<tr>
<td>G·b</td>
<td>46d</td>
<td>0.57</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>G·c</td>
<td>46v</td>
<td>-0.13</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>G·d</td>
<td>32*</td>
<td>2.12</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>G·e</td>
<td>32*</td>
<td>1.79</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>G·f</td>
<td>24</td>
<td>0.89</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>G·g</td>
<td>9*</td>
<td>3.24</td>
<td>&lt;7e-4</td>
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<tr>
<td>G·h</td>
<td>9*</td>
<td>1.88</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>G·i</td>
<td>46d</td>
<td>0.28</td>
<td>&gt;0.3</td>
</tr>
<tr>
<td>G·j</td>
<td>46v</td>
<td>-1.41</td>
<td>&gt;0.9</td>
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</table>
Locations of recording sites are as marked in Fig. 6. For Criteria 1 and 2 (Cr1 and Cr2), statistical scores are shown. For Criterion 3 (Cr3), the ratios of the epochs which met the condition are calculated for R2 and R3 (see text). Bold type indicates that the criterion was met. The significant generators which met all the criteria are marked with asterisks.
**TABLE S2** (supplemental online materials)

Transient rise after reward assessed by Criteria A, B, and C

<table>
<thead>
<tr>
<th>Recording site</th>
<th>CrA</th>
<th>CrB</th>
<th>CrC</th>
</tr>
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<tr>
<td>A·a (area 9)*</td>
<td>t=11.6, df=438, p&lt;9e–28</td>
<td>1.0</td>
<td>yes</td>
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<tr>
<td>A·b (area 46d)</td>
<td>t=4.87, df=411, p&lt;2e–6</td>
<td>0.1</td>
<td>no</td>
</tr>
<tr>
<td>A·c (area 46v)</td>
<td>t=1.87, df=414, p&gt;0.06</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>A·d (area 9)*</td>
<td>t=12.8, df=518, p&lt;1e–32</td>
<td>0.6</td>
<td>yes</td>
</tr>
<tr>
<td>A·e (area 46d)</td>
<td>t=4.46, df=362, p&lt;2e–5</td>
<td>0.0</td>
<td>no</td>
</tr>
<tr>
<td>A·f (area 46v)</td>
<td>t=2.53, df=333, p&lt;0.02</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>B·a (area 9)*</td>
<td>t=12.6, df=488, p&lt;9e–32</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>B·b (area 9)</td>
<td>t=6.33, df=373, p&lt;8e–10</td>
<td>0.0</td>
<td>yes</td>
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<tr>
<td>B·c (area 9)</td>
<td>t=10.4, df=501, p&lt;4e–23</td>
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<tr>
<td>B·d (area 9)</td>
<td>t=9.59, df=406, p&lt;9e–20</td>
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<tr>
<td>B·e (area 9)</td>
<td>t=2.38, df=338, p&lt;0.02</td>
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<td>t=9.00, df=461, p&lt;5e–18</td>
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<td>B·g (area 32)*</td>
<td>t=9.58, df=401, p&lt;2e–19</td>
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<td>Region (Area)</td>
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<td>q-value</td>
<td>Significance</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------</td>
<td>--------</td>
<td>--------------</td>
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<tr>
<td>B·h (area 24)</td>
<td>t=6.25, df=351, p&lt;2e−9</td>
<td>0.0</td>
<td>yes</td>
</tr>
<tr>
<td>B·i (area 9)*</td>
<td>t=13.2, df=450, p&lt;1e−33</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>B·j (area 9)*</td>
<td>t=9.34, df=404, p&lt;7e−19</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>B·k (area 6aβ)</td>
<td>t=5.37, df=360, p&lt;2e−7</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>B·l (area 46d)</td>
<td>t=6.46, df=389, p&lt;4e−10</td>
<td>0.0</td>
<td>no</td>
</tr>
<tr>
<td>B·m (area 46v)</td>
<td>t=−1.31, df=355, p&gt;0.1</td>
<td>0.0</td>
<td>no</td>
</tr>
<tr>
<td>G·a (area 9)*</td>
<td>t=4.45, df=457, p&lt;2e−5</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>G·b (area 46d)</td>
<td>t=6.65, df=460, p&lt;9e−11</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>G·c (area 46v)</td>
<td>t=2.33, df=415, p&lt;0.03</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>G·d (area 32)*</td>
<td>t=2.63, df=447, p&lt;0.01</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>G·e (area 32)*</td>
<td>t=3.92, df=443, p&lt;2e−4</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>G·f (area 24)*</td>
<td>t=2.08, df=443, p&lt;0.04</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>G·g (area 9)*</td>
<td>t=3.30, df=480, p&lt;2e−3</td>
<td>1.0</td>
<td>yes</td>
</tr>
<tr>
<td>G·h (area 9)</td>
<td>t=0.67, df=452, p&gt;0.5</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>G·i (area 46d)</td>
<td>t=8.81, df=449, p&lt;3e−17</td>
<td>1.0</td>
<td>no</td>
</tr>
<tr>
<td>G·j (area 46v)</td>
<td>t=3.25, df=419, p&lt;2e−3</td>
<td>0.0</td>
<td>no</td>
</tr>
</tbody>
</table>
For Criterion A (CrA), statistical scores are shown. For Criterion B (CrB), ratios of the epochs which met the condition are calculated for R4 (see text). For Criterion C (CrC), whether it was met is noted. Other formats are the same as in Table S1.
Figure 1
Tsujimoto et al.
DFT

Time series data of \(S-D\) potentials

- **Trial 1**
- **Trial 2**
- **Trial 3**
- **Trial N**

Segment data into epochs by moving \(t\) in 0.1 s steps

Fourier series data

- **Power spectra**
  - in time region \(A\)
  - (per trial basis)

- **Mean power spectrum**
  - in time region \(A\)

Complex Fourier series

The Rayleigh statistic \(R\) for the phase relative to epoch \((\phi)\)

Cortex

Active source between \(S\) and \(D\) electrodes

Current spread from a remote source

**Phase relative to epoch \((\phi)\)**

- \(\phi = 0\)
- \(\phi = 0.5\pi\)
- \(\phi = \pi\)
- \(\phi = -0.5\pi\)

E

Time series data of two potentials

- \(X=S\) or \(Y=D\) (area 32)
- \(X=S-D\) (area 9)

Segment data into epochs by moving \(t\) in 0.1 s steps

Fourier series data

- Complex Fourier series for \(X\)
- Complex Fourier series for \(Y\)
- Coherence spectrum
- Phase spectrum

The Rayleigh statistic \(R\) for the phase difference \((\phi_X - \phi_Y)\)
Figure 3
Tsujimoto et al.
Figure 4

Tsujimoto et al.

A) Monkey B

B) Monkey G

C) Area 32

D) Area 9

E) Grand mean power spectra
   Area 32 (Monkey B+G, n=4)

F) Grand mean power spectra
   Area 9 (Monkey A+B+G, n=16)
Theta power change

<table>
<thead>
<tr>
<th>Monkey</th>
<th>A</th>
<th>B</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not significant</td>
<td>◇</td>
<td>△</td>
<td>◯</td>
</tr>
<tr>
<td>Significant</td>
<td>◇</td>
<td>△</td>
<td>◯</td>
</tr>
<tr>
<td>Gradual increase</td>
<td>◇</td>
<td>△</td>
<td>◯</td>
</tr>
<tr>
<td>Rewarded vs. unrewarded</td>
<td>◇</td>
<td>△</td>
<td>◯</td>
</tr>
<tr>
<td>Both of above</td>
<td>◇</td>
<td>△</td>
<td>◯</td>
</tr>
</tbody>
</table>

* not significant in the second measurement
Figure 6
Tsujimoto et al.

**Theta power change**

<table>
<thead>
<tr>
<th></th>
<th>Monkey A</th>
<th>Monkey B</th>
<th>Monkey G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradual increase</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Rewarded vs. unrewarded</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Both of above</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Not significant
- Significant

* not significant in the second measurement (Monkey G-f)
Figure 7
Tsujimoto et al.
Figure 8

Tsujimoto et al.

Reward delivery
Movement onset

Monkey A
(4.9 Hz)

Monkey B
(5.9 Hz)

Monkey G
(5.9 Hz)

Area 9 (ipsi)
Area 9 (contra)
Area 32

95% confidence limit (corrected)