Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 11748–11751, November 1994
Neurobiology

Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding

(cognition/perception/auditory system/magnetoencephalography)

M. JOLIOT*†, U. RIBARY*, AND R. LLINÁS*‡

*Center for Neuromagnetism, Department of Physiology and Biophysics, New York University Medical Center, New York, NY 10016; and †Service Hospitalier Frederic Joliot, Département de Recherche en Imagerie, Pharmacologie et Physiologie, Commissariat à l'Energie Atomique, Orsay, France

Contributed by R. Llinás, August 10, 1994

ABSTRACT **Spontaneous oscillatory electrical activity at a frequency near 40 Hz in the human brain and its reset by sensory stimulation have been proposed to be related to cognitive processing and to the temporal binding of sensory stimuli. These experiments were designed to test this hypothesis and to determine specifically whether the minimal interval required to identify separate auditory stimuli correlates with the reset of the 40-Hz magnetic signal. Auditory clicks were presented at varying times, while magnetic activity was recorded from awake human subjects. Experimental and modeling results indicate a stimulus-interval-dependent response with a critical interval of 12–15 ms. At shorter intervals only one 40-Hz response, to the first stimulus, was observed. With longer intervals, a second 40-Hz wave abruptly appeared, which coincided with the subject's perception of a second distinct auditory stimulus. These results indicate that oscillatory activity near 40 Hz represents a neurophysiological correlate to the temporal processing of auditory stimuli. It also supports the view that 40-Hz activity not only relates to primary sensory processing, but also could reflect the temporal binding underlying cognition.**

The auditory system is known for its excellent time resolution, in contrast to the visual system, which has a delay that is deeply embedded in the integration time for the retinal system. It must be remembered that to localize sound in space the auditory system must be able to detect delays on the order of microseconds. In addition, neuropsychological and psychophysical observations indicate that the auditory system is capable of tonality discrimination of two stimuli that are separated by only 1–2 ms (1), whereas 15–20 ms is required for the perceptual separation of two stimuli (2).

Magnetic and electric recordings from the human brain have revealed spontaneous coherent oscillatory activity near 40 Hz (3, 4). This activity, which is reset by sensory stimulation (4–8), has been proposed to be related to cognitive processing (9, 10) and to the temporal binding of sensory stimuli (4).

To find whether the 40-Hz oscillatory activity relates to the temporal binding of sensory stimuli, a 37-channel magnetoencephalography (MEG) system (4) was used. In these experiments the reset of 40-Hz oscillatory activity occurring in response to one or two auditory clicks (presented at 3- to 30-ms interstimulus intervals) was studied in nine men, 22–51 years old, with normal hearing.

METHODS

A multichannel MEG system (Biomagnetic Technologies, San Diego), comprising a magnetically shielded room, a cryogenic Dewar flask with 37 magnetic sensors, and a sensor-position indicator (to determine position and orientation of the sensors with respect to the head), was used for all experiments. The subjects were asked to lie on a bed with their eyes closed and to stay attentive. The magnetic-sensor array was positioned over the auditory area of the right hemisphere.

Subjects were instructed to attend to 10 blocks of auditory stimuli. Two blocks included a repetition of one stimulus, and 8 blocks a repetition of two stimuli. The pairs had interstimulus intervals of 3, 6, 9, 12, 15, 18, 24, or 30 ms. The order of the block presentation was randomized, but the interstimulus interval for the pairs was constant during each block. The stimuli were clicks (10-kHz square wave, intensity near 60-decibel sound pressure level) presented binaurally. Stimulus pairs were presented with interstimulus-pair intervals of 130 ± 10 ms. MEG activity was recorded from 10 ms before to 100 ms after the onset of the first stimulus (bandpass, 1–400 Hz; sample rate, 1041 Hz). At the end of each block the subject reported whether the auditory stimuli comprised one or two events. During each block presentation a total of 1000 epochs were recorded and the transient responses were averaged by using the onset of the first stimulus as a trigger.

During the perceptual test each subject was presented with six sets of two click presentations with interstimulus intervals of 3, 6, 9, 12, 15, 18, 21, 24, or 30 ms. In each set the rate of presentation was the same as during the MEG recording but was repeated for a period of ≈10 s. At the end of each trial the subjects reported whether the auditory stimuli could be identified as consisting of one or two clicks. In each set a lower threshold was defined as the last "one click" answer while going through the set from 3- to 30-ms time interval. The upper threshold was defined as the last "two clicks" answer while going from 30 to 3 ms. For each set the upper and lower thresholds were averaged, and the mean perceptual threshold for all 6 sets was computed.

Simulations are based on data obtained by the single-click experiment for the first response. The second response was simulated in two ways by shifting the wave form produced by the single-click experiment by an appropriate time interval, consistent with the interstimulus interval. This was done in two ways. *Method A:* In the dependent model the response to the second click appeared only after interstimulus intervals greater than a certain value (a time threshold). This dependent model was implemented by introducing a step-function scaling factor such that the amplitude of the response for the second click was 0 for interstimulus intervals shorter than "threshold" and 1 for those longer than "threshold." *Method B:* In the independent model, the response to the second click was the same for all the interstimulus intervals. Accordingly to our definition the scaling factor of this re-

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviation: MEG, magnetoencephalography.

‡To whom reprint requests should be addressed at: Department of Physiology and Biophysics, New York University Medical Center, 550 First Avenue, New York, NY 10016.

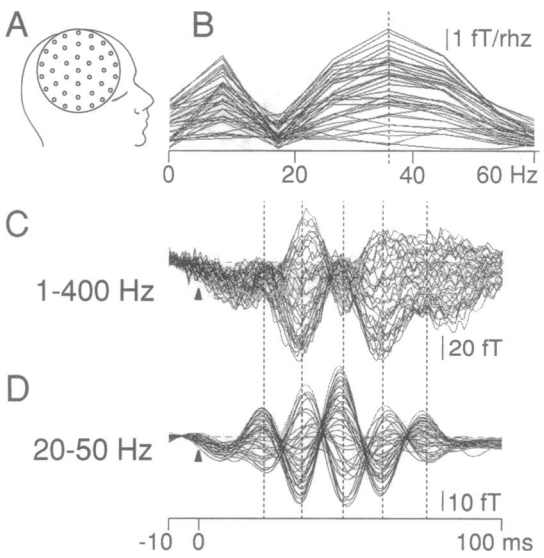

FIG. 1. Average magnetic responses recorded from a representative subject and power spectrum (1000 epochs) after binaural auditory stimulation [10 kHz, 60-decibel (sound pressure level) click]. (*A*) Schematic diagram of the sensor distribution over the right hemisphere. (*B*) Superposition of the power spectra and responses recorded from the 37 positions. Individual traces show a clear activation near 40 Hz. (*C*) Band-pass filtering from 1 to 400 Hz. The 40-Hz activity is visible in addition to a small low-frequency activation (arrowhead indicates stimulus onset). (*D*) Twenty- to 50-Hz filtering isolates only the 40-Hz events. Broken lines indicate peak latencies. For this subject the mean latencies were 20.8, 34.2, 47.6, 64.4, and 75.6 ms (SD = 0.63 ms, $n = 5$) as measured in a replicate experiment.

sponse was constantly 1. Method A was fitted to the data by using a local optimizer (11) in a single global fit on the eight recording sets. The criterion (χ) was a none-weight sum of the square difference of the data to the model computed for all 37 channels from the time epoch between 21 and 100 ms. In method B no parameters were computed since this model supposed that a response would be elicited independently of the interstimulus interval.

RESULTS AND DISCUSSION

A power spectral analysis of the raw data (Fig. 1) revealed a significant component near 40 Hz, indicating the presence of a synchronized 40-Hz event in the human brain (5, 7, 8). The data were filtered at 20–50 Hz for further analysis to remove a 10-Hz component, which modified the baseline in the raw data in each of the 37 channels differently, depending on the 10-Hz component in that particular channel. The high-frequency rhythm near 40 Hz in the raw data was well correlated with the 40-Hz response in the filtered data. We define the 40-Hz response produced by a single stimulus as a 2.5 oscillatory cycle, demonstrating two and one-half oscillations at 40 Hz.

Magnetic recordings demonstrated a single 40-Hz response following the presentation of two auditory stimuli at interstimulus intervals < 12 ms. Indeed, the response was identical to that following a single stimulus (Fig. 2). When the stimuli were presented at longer intervals, a second response abruptly appeared which overlapped with that elicited by the first stimulus.

To investigate the mechanism underlying these results, we tested two possible propositions. The first (Fig. 3*A*) posited that (*i*) the first stimulus triggers a 40-Hz oscillatory event and (*ii*) the second stimulus would induce a similar response only after a given time interval. The second model (Fig. 3*B*) posited that both stimuli induce 40-Hz activity, independently of interstimulus interval.

The results predicted by the two models were compared with the electrophysiological data obtained from all 37 recording positions (Fig. 3 *C* and *D*). Statistical analysis of all nine subjects indicated that the first model fitted the experimental data significantly better than the second (χ^2 test for stimulus intervals ≤ 14.2 ms; Fig. 3 *E* and *F*). An equivalent individual subject measurement of this critical interstimulus interval (Fig. 4) was given by the first model, and its mean across the nine subjects was found to be 15.00 ms (SD = 2.6

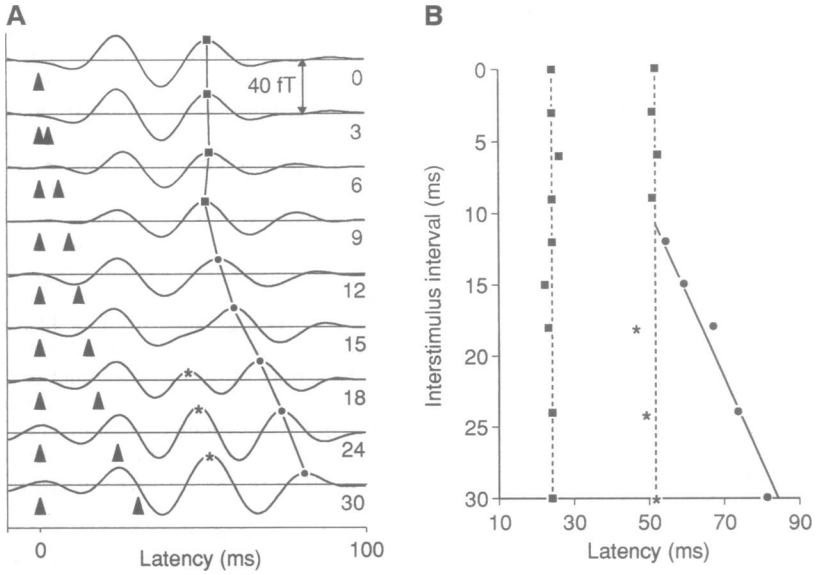

FIG. 2. Effect of increasing the interstimulus interval on MEG activity. (*A*) The largest of the 37 responses, obtained by the single-click experiment and filtered at 20–50 Hz, was selected and that same channel recording is the actual one illustrated in each block. Arrowheads indicate the onset of the clicks, and the number to the right gives the interstimulus interval in milliseconds. (*B*) The peak latencies of the responses shown on the left are plotted as a function of interstimulus interval. The broken lines indicate the peak latencies for the response to the single click. Note that the response latencies for intervals < 12 ms are similar to those for a single stimulus. As the interval increased, a second 40-Hz response was observed (solid line). The dots indicate the interaction between the second peak of the first response and the second peak of the second response. Asterisks indicate the interaction between the second peak of the first response and the first peak of the second response.

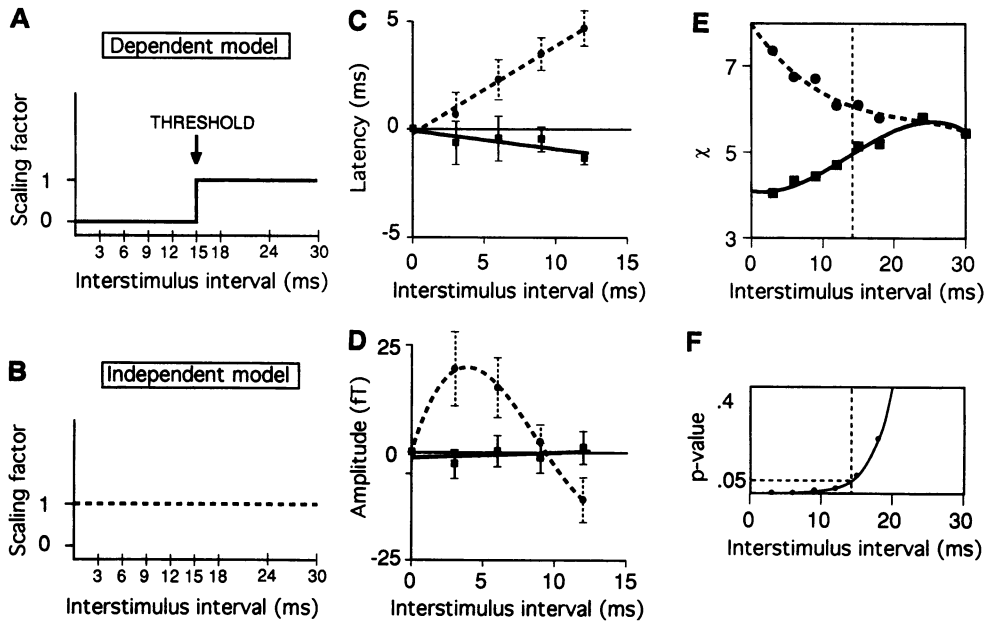

FIG. 3. Independent and dependent models for the response to a second stimulus. (*A*) In the dependent model the response to the second click appears only after interstimulus intervals greater than a certain value (a time threshold). (*B*) In the independent model the response to the second click is the same for all the interstimulus intervals. (*C* and *D*) Superposition of the mean difference (±2 SEM) across all the subjects ($n = 9$) of the dependent model and the data (solid line and ■) and of the independent model and the data (broken line and ●) for the response latency (*C*) and response amplitude (*D*). For each subject data were taken from the first four peaks of the response. (*E*) Plot of the mean value for nine subjects of the criterion χ computed separately for each recording set. For interstimulus intervals <14.2 ms the dependent model (solid line and ■) showed significantly lower χ values than the independent model (broken line and ●) (two-tailed paired *t* test on the χ values of each different recording block). (*F*) The *P* values for the eight *t* tests.

ms). As expected, this was slightly greater than the value produced by the global statistical analysis (Fig. 3).

This finding indicates that at interstimulus intervals ≤ 14.2 ms, only the first stimulus induced a 40-Hz response, while with longer intervals each stimulus induced its own 40-Hz activity. Although we use a simple model to describe this phenomenon, physiologically the abruptness of the response probably relates to nonlinear single-cell oscillatory properties as observed *in vitro* and *in vivo* (12, 13).

A similar set of stimuli were presented following MEG recordings, and the perceptual threshold for identifying two clicks was established (Fig. 4). Perceptual response from all subjects indicated that stimuli presented at an interstimulus interval > 13.7 ms could be identified as two clicks. The interval between stimuli required for the second MEG response and that required for the recognition of a second auditory stimulus as a distinct event were not statistically different (interval difference = 1.32 ms, $n = 9$, $P = 0.309$, two-tailed Student *t* test). No regression between the two variables was significant, indicating a cluster-like correlation near 12–15 ms.

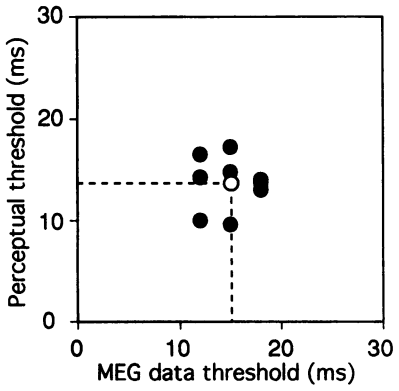

FIG. 4. Relationship between perceptual and MEG "threshold" for identifying two clicks (minimum interstimulus interval). The graph plots the thresholds for each of the nine subjects (●) and the mean across all subjects (○).

These findings correlate well with neuropsychological and psychophysical observations. The ability to judge the temporal order of a sequence of sounds was reported to depend on whether the task required actual identification of the individual elements of the sequence or whether it could be performed by discrimination of their global pattern (14). While the finest acuity for discrimination tasks is on the order of 1–2 ms (1), the identification of individual element is on the order of 15–20 ms (2). The present results coincide closely to the classical interstimulus interval required to identify individual stimuli (2). It must also be emphasized that delivering double stimuli at intervals < 12–15 ms did change the tonality of the perceived sound. This actually indicates that stimuli coming within one perceptual "quantum" (12–15 ms) are actually bound into one cognitive event rather than perceived as separate entities. In addition, other observations led to the conclusion that sensory information is processed in discrete time segments (15, 16) as low as 12 ms (17).

Our findings suggest that 40-Hz oscillatory activity not only is involved in primary sensory processing *per se* but also forms part of a time conjunction or binding property that amalgamates sensory events occurring in perceptual time quanta into a single experience (4). Indeed, 40-Hz oscillatory activity is prevalent in the mammalian central nervous system (18–23), as evidenced at both the single-cell (12, 13) and multicellular (5, 7, 8, 24) levels. This oscillatory activity, which may also be studied by electrical recording (3, 10), has been viewed as a possible mechanism for the conjunction of spatially distributed visual sensory activity (25) or multiregional cortical binding (9, 24). In addition, it provides a significant window for clinical investigation (7, 26). Our presented findings suggest that binding could occur in steps or "quanta" of 12–15 ms and further support our hypothesis that 40-Hz oscillatory activity could serve a broad cognitive binding function (4).

We acknowledge support from the Charles A. Dana Foundation, technical assistance by R. Jagow and Dr. E. Kronberg (Center for Neuromagnetism), and B. Mazoyer (Xavier Bichat School of Medicine, Paris) for statistical assistance.

1. Miller, G. A. & Taylor, W. G. (1948) *J. Acoust. Soc. Am.* **20,** 171–182.
2. Hirsh, I. J. (1959) *J. Acoust. Soc. Am.* **31,** 759–767.
3. Sheer, D. E. (1989) in *Brain Dynamics,* eds. Basar, E. & Bullock, T. H. (Springer, Berlin), pp. 339–374.
4. Llinás, R. & Ribary, U. (1993) *Proc. Natl. Acad. Sci. USA* **90,** 2078–2081.
5. Galambos, R., Makeig, S. & Talmachoff, P. J. (1981) *Proc. Natl. Acad. Sci. USA* **78,** 2643–2647.
6. Basar, E., Rosen, B., Basar-Eroglu, C. & Greitschus, F. (1987) *J. Neurosci.* **33,** 103–117.
7. Ribary, U., Ioannides, A. A., Singh, K. D., Hasson, R., Bolton, J. P. R., Lado, F., Mogilner, A. & Llinás, R. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 11037–11041.
8. Pantev, C., Makeig, S., Hoke, M., Galambos, R., Hampson, S. & Gallen, C. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 8996–9000.
9. Llinás, R. & Ribary, U. (1992) in *Induced Rhythms in the Brain,* eds. Basar, E. & Bullock, T. (Birkhäuser, Boston), pp. 147–154.
10. Tiitinen, H., Sinkkonen, J., Rainikainen, K., Alho, K., Lavikainen, J. & Naatanen, R. (1993) *Nature (London)* **364,** 59–60.
11. Marquardt, D. W. (1963) *J. Soc. Ind. Appl. Math.* **11,** 431–441.
12. Llinás, R., Grace, A. A. & Yarom, Y. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 897–901.
13. Steriade, M., Curro Dossi, R., Pare, D. & Oakson, G. (1991) *Proc. Natl. Acad. Sci. USA* **88,** 4396–4400.
14. Moore, B. C. J. (1993) *Ann. N.Y. Acad. Sci.* **682,** 119–136.
15. Poppel, E. (1970) *Psychol. Forsch.* **34,** 1–9.
16. Madler, C., Keller, I., Schwender, D. & Poeppel, E. (1991) *Br. J. Anaesth.* **66,** 81–87.
17. Kristofferson, A. B. (1984) *Ann. N.Y. Acad. Sci.* **423,** 3–15.
18. Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M. & Reitboeck, H. J. (1988) *Biol. Cybern.* **60,** 121–130.
19. Gray, C. M. & Singer, W. (1989) *Proc. Natl. Acad. Sci. USA* **86,** 1698–1702.
20. Freeman, W. J. (1975) *Mass Action in the Nervous System* (Academic, New York).
21. Freeman, W. J. (1992) in *Induced Rhythms in the Brain,* eds. Basar, E. & Bullock, T. (Birkhäuser, Boston), pp. 183–199.
22. Ahissar, E. & Vaaida, E. (1990) *Proc. Natl. Acad. Sci. USA* **87,** 8935–8939.
23. Murthy, V. N. & Fetz, E. E. (1992) *Proc. Natl. Acad. Sci. USA* **89,** 5670–5674.
24. Bressler, S. L., Coppola, R. & Nakamura, R. (1993) *Nature (London)* **366,** 153–156.
25. Crick, F. & Koch, C. (1990) *Cold Spring Harbor Symp. Quant. Biol.* **55,** 953–962.
26. Ribary, U., Llinás, R., Kluger, A., Suk, J. & Ferris, S. H. (1989) in *Advances in Biomagnetism,* eds. Williamson, S. J., Hoke, M., Stroink, G. & Kotani, M. (Plenum, New York), pp. 311–314.