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An Allometric Analysis of the Frequency of Hippocampal Theta: The Significance of Brain Metabolic Rate

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Abstract. The dominant frequency of hippocampal rhythmic slow activity (RSA) is known to differ among species, even under similar experimental conditions. The cause of these species differences has not yet been identified. In this paper it is shown that RSA frequency is allometrically related to brain size for the 9 mammalian species for which data are available. It is further shown that the relationship between brain size and RSA frequency is similar to the relationship between brain size and specific brain metabolic rate. Based on these and other relationships, it is suggested that differences in the firing frequencies of the neuronal pacemakers underlying the generation of RSA reflect differences in specific brain metabolic rate, both within and among species.

It is widely known that the pacing of physiological events in small mammals is faster than the pacing of physiological events in large mammals. Out of this recognition has come the concept of physiological time, a concept that refers to a variable time scale for relating physiological events in mammals of different sizes [Lindstedt and Calder, 1981]. The most important indicator of the flow of physiological time is the rate at which an animal consumes energy, i.e. its metabolic rate per unit of body mass (or specific metabolic rate) [Schmidt-Nielsen, 1984]. Consequently, physiological time flows faster (relative to real time) for small mammals than for large mammals because the specific metabolic rate is higher in small mammals than in large mammals. Specifically, the specific metabolic rate decreases 25% with each log unit increase in body mass or, stated differently, $y = ax^{-0.25}$, where y is the specific metabolic rate, x is body mass, and a is a constant [for reviews, see Schmidt-Nielsen, 1984; Peters, 1983]. The implications of this relationship are many. For example, cyclic events such as heartbeat frequency and respiratory frequency also scale to body mass to the –0.25 power; these relationships are most likely the result of the tuning of the body's oxygen delivery systems to the energy needs of the animal [Kleiber, 1961]. In addition, the metabolic rate is a limiting factor for many life history variables including growth, longevity, reproduction and feeding strategies [Eisenberg, 1981; Hofman, 1983]. In other words, the rate of energy expenditure constrains the development and activity of an animal.

Of course, the metabolic rate of a complete animal is the sum of the metabolic rates of its individual components. And as one would expect, the specific metabolic rates of individual organs, similar to the specific metabolic rate of the body, decrease with increasing body size [Schmidt-Nielsen, 1984]. The brain is no exception. On the basis of five published reports on the oxygen consumption of the brains of 5 different species of mammals, Mink et al. [1981] determined that the specific brain metabolic rate decreases with the –0.13 power of brain mass (or to the –0.16 power of body mass for these particular 5 species). In addition, glucose utilization, using the 2-deoxyglucose technique, has been measured within 25 select brain regions in rats, cats and rhesus monkeys [Sokoloff, 1984]. In 23 of these 25 brain regions, glucose utilization per unit brain mass decreases with increasing brain size. The causes of this allometric decrease in specific brain metabolic rate are not known; it is pos-

sible, however, that individual neurons, similar to individual cells in the liver [Smith, 1956], have allometric decreases in mitochondrial density and, thus, metabolism with increasing body size. Of course, the additional influences of neuron density and the neuron/glia ratio cannot be ignored when addressing the question of cerebral metabolism [Tower and Young, 1973].

If the decrease in specific brain metabolic rate with increasing brain size reflects a similar decrease in neuronal metabolism and activity with increasing brain size, one might expect the consequences of this relationship to show up in the electrophysiological activity of the brain. Specifically, the relatively low specific metabolic rates of large brains may be associated with some diminution of electrophysiological activity, and, conversely, the relatively high specific metabolic rates of small brains may be associated with some augmentation of electrophysiological activity. Determining whether such allometric relations exist requires that we identify an electrophysiological phenomenon that (a) has been studied in a number of mammalian species of different sizes and (b) has been recorded under similar conditions in these different species. The theta rhythm of the hippocampus fulfills those requirements.

The theta rhythm (or rhythmical slow activity; RSA) of the hippocampus has been the focus of numerous investigations for 35 years. One goal of these investigations has been the determination of the role of RSA in brain function and animal behavior. This task has been complicated by the fact that RSA of any given frequency has different behavioral correlates in different species. Consequently, many hypotheses regarding the 'function' of RSA have been suggested, including roles in locomotion [e.g. Vanderwolf, 1969], orientation [e.g. Grastyan et al., 1966], arousal [Green and Arduini, 1954], attention [Bennett et al., 1973] and memory [Olton and Samuelson, 1976].

There appear to be two different RSA-producing neural 'systems', and each can be distinguished on the basis of RSA frequency and its behavioral correlates, as well as by pharmacological manipulation. One system produces relatively high-frequency RSA in association with motor behaviors such as walking, running and rearing (designated mobility-related theta or MRSA), while the other system produces relatively low-frequency RSA when the same animal is alert but completely immobile (designated immobility-related theta or IRSA). All species studied thus far produce MRSA, whereas only some of these same species produce IRSA [Robinson, 1980]. Species also differ in that some mammals (e.g. rats and gerbils) produce higher frequency RSA than other mammals (e.g. cats and dogs) under similar experimental conditions. The cause of these frequency differences has not yet been identified; that cats and dogs are larger mammals than rats and gerbils suggests an allometric effect. A number of questions arise. First, is an allometric relationship between RSA frequency and brain size apparent when all species studied are included in the analysis and when the experimental conditions are comparable? Second, if so, is the slope of the regression line similar to that relating specific brain metabolic rate to brain mass? And third, if the two allometric relationships are similar, what can account for the similarity?

Method

The literature on hippocampal RSA was searched for those articles reporting the dominant frequency of hippocampal RSA during specified behaviors. As stated above, all species studied thus far show RSA when mobile, whereas only some species (e.g. rabbits, cats) show RSA when immobile [Robinson, 1980]. Thus, only MRSA was analyzed. Behaviors included in this category are walking, running, exploration, 'early orienting' [Brown, 1968], pedal pressing and other gross body movements.

Typical values for MRSA frequency were determined for 9 species from the literature. Data were available for mice *(Mus musculus)*, hamsters *(Mesocricetus auratus)*, gerbils *(Meriones unguiculatus)*, rats *(Rattus norvegicus)*, guinea pigs *(Cavia porcellus)*, rabbits *(Oryctolagus cuniculus)*, cats *(Felis sylvestris)*, dogs *(Canis familiaris)* and humans *(Homo sapiens;* see table 1). In every species but hamsters, gerbils and humans, more than one article was available that specified MRSA frequency. Articles were omitted from analysis if MRSA frequency was reported as a range greater than 1 Hz in order to reduce the probability of incorrectly estimating the 'true' frequency; when a frequency range was used, the midpoint was taken as the representative frequency. If the same author(s) had more than one publication for a given species, then a value for RSA frequency was taken from one representative publication. For example, all the work on hippocampal RSA in dogs is attributable to two research groups; thus one value for RSA frequency from each group was chosen for this analysis. In some cases, the same research group did similar work on two different species so that inclusion of these data allowed for some control over variability due to the different experimental techniques found in different laboratories. In every report included in this analysis, MRSA was recorded using electrodes implanted in the hippocampus.

Special mention should be made of the human data. Arnolds et al. [1980] report MRSA in 1 human female suffering from epilepsy. Although an epileptic patient is not an ideal subject for the determination of a species-typical RSA frequency, epilepsy provides the only justification for the implantation of electrodes in the human hippocampus. Nonhuman primates have been studied, but diffi-

Table 1. Summary table of reports of movement-related theta included in this analysis

Species	Brain mass, g	Theta frequency, Hz	Behavioral correlate	Reference
Mouse	0.40	7.86 8.8	walking running	Caudarella et al., 1987 Frederickson et al., 1982
Gerbil	1.0	7.7	running	Whishaw, 1972
Hamster	1.1	8.13–8.70	exploratory sniffing	Macrides, 1975
Rat	3.3	8.2 8.0–8.3	motor movements walking, rearing	Sainsbury et al., 1987 Vanderwolf, 1969
Guinea pig	4.0	8	motor movements	Montoya and Sainsbury, 1985
Rabbit	9.8	8 8.3 8	hopping hopping motor movements	Kramis et al., 1975 Whishaw, 1976 Harper, 1971
Cat	28.4	5.0 4.7 5.4–5.8	approach early orienting walking	Bennett and French, 1977 Brown, 1968 Frederickson et al., 1978
Dog	70	5.1 4.5	walking pedal pressing	Arnolds et al., 1979 Black and Young, 1972
Human	1,250	3.3	walking	Arnolds et al., 1980

Values for brain mass from Martin and Harvey [1985].

culty in detecting RSA in these animals has led some to argue that it does not exist. The success of Arnolds and his colleagues in recording RSA in their human subject suggests that other investigators failed to detect RSA for technical reasons, perhaps due to inadequate placement of electrodes [for a discussion of this problem, see Robinson, 1980]. In addition, the characteristics of RSA in the patient were orderly, repeatable and in some respects similar to the same researchers' findings in dogs [Arnolds et al., 1979]. Nonetheless, it remains possible that RSA frequency in this patient was significantly different from that of normal humans.

The constitutional variable used in this analysis is brain mass, values of which were taken from a standard table [Martin and Harvey, 1985]. Prior to regression analysis, brain mass and MRSA frequency were transformed logarithmically in order to normalize their distributions.

Finally, it should be pointed out that family level analysis is more appropriate than species level analysis in comparative studies, the reason being that the majority of variance in most constitutional variables lies at the family level and above [Harvey and Mace, 1982; Elgar et al., 1988]. Nonetheless, the species will here be considered the unit of analysis because of the very small sample size available for analysis of hippocampal RSA.

Results

Table 1 presents, for each species, the value(s) of MRSA frequency included in this analysis as well as the behavior observed during the recording of MRSA. Values of brain mass are also presented. It can be seen that, whereas brain mass increases by approximately 4 orders of magnitude from mouse to human, MRSA frequency decreases by a factor of approximately 2.5 over the same range.

The linear regression of RSA frequency on brain mass is shown in figure 1. The correlation coefficient (r) of 0.923 is highly significant ($p < 0.0005$). The regression is defined by the power equation $y = 8.6x^{-0.124}$, where y is RSA frequency in Hertz, and x is brain mass in grams. The slope of the regression line, −0.124, has a 95% confidence interval ranging from −0.078 to −0.171.

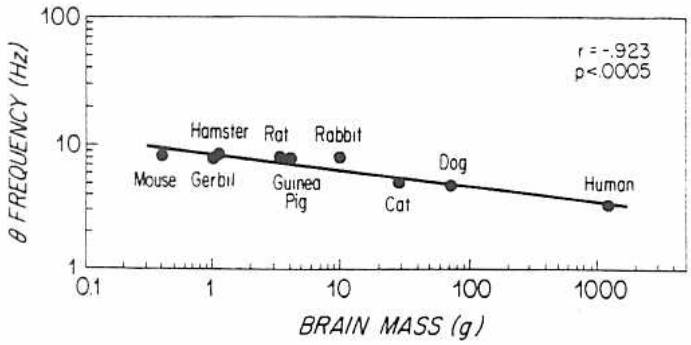

Fig. 1. Movement-related theta frequency (Hz) versus brain mass (g) for 9 species of mammals. The best-fit line is shown and is described by the equation $y = 8.6x^{-0.124}$. The slope of -0.124 has a 95% confidence interval ranging from -0.078 to -0.171.

Discussion

The analysis of data independently gathered in various species necessarily entails a number of methodological difficulties, especially when laboratory studies are involved [Elgar et al., 1988]. In the case of research on hippocampal RSA, investigators have used a variety of electrophysiological techniques, behavioral tests and environmental conditions in their studies. Despite these and other potential sources of variability, figure 1 strongly suggests that RSA frequency is allometrically related to brain size. This is the first such relationship to be identified for an electrophysiological phenomenon.

The mass exponent for the regression equation relating RSA frequency to brain mass (i.e. -0.124) is notable. With a 95% confidence interval ranging from -0.078 to -0.171, it cannot be distinguished statistically from the mass exponent relating specific brain metabolic rate to brain mass (i.e. -0.13) as reported by Mink et al. [1981]. It is important to emphasize, however, that the allometric relations for both RSA frequency and specific brain metabolic rate are based on very small sample sizes; consequently, conclusions based on them must be drawn cautiously. In addition, the inclusion of human data points in small data sets can distort the 'true' relationship for mammals because of the tendency of human data points to deviate significantly from their expected values. For the moment, all one can say is that the allometry of RSA frequency is consistent with the hypothesis that RSA frequency is associated with the rate at which energy is consumed by the brain.

Assuming that a relationship does exist between specific brain metabolic rate and RSA frequency, through what channels is this relationship expressed? The answer to this question may lie in the fact that hippocampal RSA is generated by pacemaker neurons located within the medial septum and diagonal band of Broca [for a review, see O'Keefe and Nadel, 1978]. Pacemaker neurons underlie the generation of other slow wave rhythms as well, such as that recorded in the olfactory bulb in rabbits [Chaplain, 1976]. Furthermore, the biochemical mechanism underlying the firing of pacemaker neurons within the olfactory bulb is metabolic in nature, as evidenced by the fact that inhibitors of intermediary metabolism abolish slow wave activity [Chaplain, 1976, 1979]. The implication for hippocampal RSA is clear: if the lower specific brain metabolic rates of larger mammals are a reflection of lower firing frequencies of neurons in general and of the RSA pacemaker cells in particular, then RSA frequency in larger mammals should be lower than RSA frequency in smaller mammals, as demonstrated here. Whether similar relations exist for other electrophysiological phenomena remains to be determined.

If specific brain metabolic rate correlates with RSA frequency across species, then one would expect these two variables to be correlated within a species. Indirect evidence in support of this suggestion is provided by experiments in which body temperature as well as specific brain metabolic rate or RSA frequency were monitored in rats. Whishaw and Vanderwolf [1971] monitored the hippocampal EEG and body temperature while rats were walking and found that over a body temperature range of 24–42 °C, RSA frequency increases linearly with body temperature. In addition, RSA frequency increases 'slightly more than 2-fold' when body temperature is raised by 10 °C. In other words, RSA frequency has a Q_{10} approximately equal to 2 over the temperature range tested. Similar relationships have been found between body temperature and specific brain metabolic rate. For example, Hagerdal et al. [1975] measured the cerebral metabolic rate for oxygen in rats and found that over a body temperature range of 27–37 °C the cerebral metabolic rate per unit body mass also increases linearly with temperature and has a Q_{10} of 2. To sum up, RSA frequency correlates with specific brain metabolic rate – across species and within species.

Finally, although we are far from fully delineating

the roles of the hippocampus in brain function, its importance for sensory processing and memory storage seems well established [for a review, see O'Keefe and Nadel, 1978]. To the extent that RSA reflects the actual functioning of the hippocampus, it appears that mammals of different sizes may process information at different speeds. If true, one implication is that not only does physiological time pass more quickly for smaller mammals, but psychological time may as well. The inconstancy of psychological time within humans alone is supported by the common observation that inebriation causes a profound alteration of psychological time. If psychological time varies within individual humans, then it seems reasonable to suggest that it also varies across different species. William James [1893] argued for such a notion when he wrote that 'we have every reason to think that creatures may possibly differ enormously in the amounts of duration which they intuitively feel and in the fineness of the events that may fill it'. To James' intuition can be added the following hypothesis: not only may mammals differ in their perception of temporal duration but such differences may be allometrically related to size and may be associated with the rates at which different-sized brains consume energy.

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References

Arnolds, D.E.A.T.; Lopes da Silva, F.H.; Aitink, J.W.; Kamp, A.: Hippocampal EEG and behaviour in dog. II. Hippocampal EEG correlates with elementary motor acts. Electroencephalogr. Clin. Neurophysiol. *46:* 571–580 (1979).

Arnolds, D.E.A.T.; Lopes da Silva, F.H.; Aitink, J.W.; Kamp, A.; Boeijinga, P.: The spectral properties of hippocampal EEG related to behaviour in man. Electroencephalogr. Clin. Neurophysiol. *50:* 324–328 (1980).

Bennett, T.L.; French, J.: Electrical activity of the cat hippocampus during the species-typical gape response: evidence against the voluntary movement hypothesis. Behav. Biol. *21:* 432–437 (1977).

Bennett, T.L.; Herbert, P.N.; Moss, D.E.: Hippocampal theta activity and the attention component of discrimination learning. Behav. Biol. *8:* 173–181 (1973).

Black, A.H.; Young, G.A.: Electrical activity of the hippocampus and cortex in dogs operantly trained to move and to hold still. J. Comp. Physiol. Psychol. *79:* 128–141 (1972).

Brown, B.B.: Frequency and phase of hippocampal theta activity in the spontaneously behaving cat. Electroencephalogr. Clin. Neurophysiol. *24:* 53–62 (1968).

Caudarella, M.; Durkin, T.; Galey, D.; Jeantet, Y.; Jaffard, R.: The effect of diazepam on hippocampal EEG in relation to behavior. Brain Res. *435:* 202–212 (1987).

Chaplain, R.A.: Intracellular recordings from granule cells in the rabbit bulbus olfactorius. Neurosci. Lett. *3:* 133–137 (1976).

Chaplain, R.A.: Metabolic control of neuronal pacemaker activity and the rhythmic organization of central nervous functions. J. Exp. Biol. *81:* 113–130 (1979).

Eisenberg, J.F.: The Mammalian Radiations. The University of Chicago Press, Chicago (1981).

Elgar, M.A.; Pagel, M.D.; Harvey, P.H.: Sleep in mammals. Anim. Behav. *36:* 1407–1419 (1988).

Frederickson, C.J.; Smylie, C.S.; Howell, G.A.; Lenig, R.B.: Movement-dependent and movement-independent changes in hippocampal RSA in cats. Brain Res. Bull. *3:* 559–562 (1978).

Frederickson, C.J.; Frederickson, M.H.; Lewis, C.; Howell, G.A.; Smylie, C.; Wright, C.G.; Hubbard, D.G.: Hippocampal EEG in normal mice and in mice with congenital vestibular defects. Behav. Neural Biol. *34:* 121–131 (1982).

Grastyan, E.; Karmos, G.; Vereczkey, L.; Kellenyi, E.E.: The hippocampal electrical correlates of the homeostatic regulation of motivation. Electroencephalogr. Clin. Neurophysiol. *21:* 34–53 (1966).

Green, J.D.; Arduini, A.: Hippocampal electrical activity in arousal. J. Neurophysiol. *17:* 533–557 (1954).

Hagerdal, M.; Harp, J.; Nilsson, L.; Siesjo, B.K.: The effect of induced hypothermia upon oxygen consumption in the rat brain. J. Neurochem. *24:* 311–316 (1975).

Harper, R.M.: Frequency changes in hippocampal electrical activity during movement and tonic immobility. Physiol. Behav. *7:* 55–58 (1971).

Harvey, P.H.; Mace, G.M.: Comparisons between taxa and adaptive trends: problems of methodology. *In* Current Problems in Sociobiology (ed. by King's College Sociobiology Group) Cambridge University Press, Cambridge, pp. 346–361 (1982).

Hofman, M.A.: Energy metabolism, brain size and longevity in mammals. Quart. Rev. Biol. *58:* 495–512 (1983).

James, W.: Principles of Psychology. Harvard University Press, Cambridge (1983).

Kleiber, M.: The Fire of Life. Wiley, New York (1961).

Kramis, R.; Vanderwolf, C.H.; Bland, B.H.: Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbitol. Exp. Neurol. *49:* 58–85 (1975).

Lindstedt, S.L.; Calder, W.A.: Body size, physiological time, and longevity of homeothermic animals. Quart. Rev. Biol. *56:* 1–16 (1981).

Macrides, F.: Temporal relationships between hippocampal slow waves and exploratory sniffing in hamsters. Behav. Biol. *14:* 295–308 (1975).

Martin, R.D.; Harvey, P.H.: Brain size allometry: ontogeny and phylogeny. *In* Size and Scaling in Primate Biology (ed. by W.L. Jungers) Plenum Press, New York, pp. 147–173 (1985).

Mink, J.W.; Blumenschine, R.J.; Adams, D.B.: Ratio of central ner-

vous system to body metabolism in vertebrates: its constancy and functional basis. Am. J. Physiol. *241:* R203–R212 (1981).
Montoya, C.P.; Sainsbury, R.S.: The effects of entorhinal cortex lesions on type 1 and type 2 theta. Physiol. Behav. *35:* 121–126 (1985).
O'Keefe, J.; Nadel, L.: The Hippocampus As a Cognitive Map. Oxford University Press, Oxford (1978).
Olton, D.S.; Samuelson, R.J.: Remembrance of places passed: spatial memory in rats. J. Exp. Psychol. *2:* 97–116 (1976).
Peters, R.H.: The Ecological Implications of Body Size. Cambridge University Press, Cambridge (1983).
Robinson, T.E.: Hippocampal rhythmic slow activity (RSA; theta): a critical analysis of selected studies and discussion of possible species-differences. Brain Res. Rev. *2:* 69–101 (1980).
Sainsbury, R.S.; Heynen, A.; Montoya, C.P.: Behavioral correlates of hippocampal type 2 theta in the rat. Physiol. Behav. *39:* 513–519 (1987).
Schmidt-Nielsen, K.: Scaling: Why Is Animal Size So Important? Cambridge University Press, Cambridge (1984).
Smith, R.E.: Quantitative relations between liver mitochondria metabolism and total body weight in mammals. Ann. NY Acad. Sci. *62:* 403–422 (1956).
Sokoloff, L.: Metabolic Probes of Central Nervous System Activity in Experimental Animals and Man. Sinauer, Sunderland, Massachusetts (1984).
Tower, D.B.; Young, O.M.: The activities of butyrylcholinesterase and carbonic anhydrase, the rate of anaerobic glycolysis, and the question of a constant density of glial cells in cerebral cortices of various mammalian species from mouse to whale. J. Neurochem. *20:* 269–278 (1973).
Vanderwolf, C.H.: Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr. Clin. Neurophysiol. *26:* 407–418 (1969).
Whishaw, I.Q.: Hippocampal electroencephalographic activity in the Mongolian gerbil during natural behaviours and wheel running and in the rat during wheel running and conditioned immobility. Can. J. Psychol. *26:* 219–239 (1972).
Whishaw, I.Q.: The effects of alcohol and atropine on EEG and behavior in the rabbit. Psychopharmacol. *48:* 83–90 (1976).
Whishaw, I.Q.; Vanderwolf, C.H.: Hippocampal EEG and behavior: effects of variation in body temperature and relation of EEG to vibrissae movement, swimming and shivering. Physiol. Behav. *6:* 391–397 (1971).

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