Entrainment of Neuronal Oscillations as a Mechanism of Attentional Selection

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Entrainment of Neuronal Oscillations as a Mechanism of Attentional Selection

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Whereas gamma-band neuronal oscillations clearly appear integral to visual attention, the role of lower-frequency oscillations is still being debated. Mounting evidence indicates that a key functional property of these oscillations is the rhythmic shifting of excitability in local neuronal ensembles. Here, we show that when attended stimuli are in a rhythmic stream, delta-band oscillations in the primary visual cortex entrain to the rhythm of the stream, resulting in increased response gain for task-relevant events and decreased reaction times. Because of hierarchical cross-frequency coupling, delta phase also determines momentary power in higher-frequency activity. These instrumental functions of low-frequency oscillations support a conceptual framework that integrates numerous earlier findings.

Neuronal oscillations reflect rhythmic shifting of neuronal excitability over a wide range of spatial and temporal scales (*1*–*3*). These oscillations play a role in a variety of brain operations including stimulus processing (*2*–*4*), neuronal interactions across areas (*2*, *4*), memory formation (*5*), and cognitive control of input processing (*6*–*8*). To date, gamma-band (30 to 70 Hz) oscillations have been linked most clearly to active, attentive processes (*8*, *9*). However, recent evidence suggests that lower-frequency (theta and alpha) oscillations also contribute to active processing (*10*, *11*) and that during rhythmic stimulation, oscillatory entrainment in various frequency bands can be enhanced by attention (*12*–*14*). We therefore hypothesized that if relevant stimuli appear in a rhythmic and predictable pattern, neuronal oscillations would entrain (phase-lock) to the structure of the attended stimulus stream (*3*, *12*–*16*) and thus serve as instruments of sensory selection.

Our hypothesis makes four key predictions: (i) When attention is allocated to one of several rhythmic event streams, oscillations in the sensory cortices will entrain (phase-lock) to the events in the attended stream. (ii) Because of entrainment, rhythmic fluctuations in neuronal excitability will be aligned so that high-excitability phases will tend to coincide with events in the attended stream. Given some variability in stimulation rhythm and entrainment, (iii) neuronal response amplitude and (iv) reaction time will be systematically related to the phase of the entrained oscillation.

To test these predictions, we analyzed the effects of selective attention on the visual event–related response and the prestimulus activity obtained during 24 experimental sessions in the primary visual cortex (V1) of two macaque monkeys (*17*). Monkeys were trained to perform an intermodal selection task, as described previously (*18*). In this task (Fig. 1), interdigitated auditory and visual stimuli (beeps and flashes) were delivered with random stimulus onset asynchronies (SOAs) varying between 500 and 800 ms (Gaussian distribution), with a mean of 650 ms (1.5-Hz delta frequency) within each stream (mean combined stimulus rate of 3 Hz). Despite the variability in SOA, visual and auditory stimulus streams stayed, on average, 180° out of phase over all trials. This paradigm combines the rhythmic structure and variability characteristic of natural event patterns. In alternate trial blocks, the monkey had to attend to either the visual or the auditory stimulus stream and make a manual response to an infrequently presented "oddball" stimulus.

Laminar profiles of field potentials and concomitant multiunit activity (MUA) were recorded with linear array multielectrodes positioned to straddle the layers of V1 during each recording session. Instead of analyzing the field potentials, we calculated current-source density (CSD) profiles, which allow for better localization and more direct physiological interpretation of transmembrane currents that cause excitability changes and generate the local field potential profile. As in previous studies (*18*, *19*), the comparison of response amplitudes within each experiment revealed a significantly larger response to attended visual stimuli: On average, CSD response amplitude was 62% higher and MUA was 46% larger in the attend visual (AV) condition, as compared with the attend auditory (AA) condition (fig. S1).

To illustrate differential entrainment by attention [prediction (i)], we compared averaged CSD profiles in the AV and AA conditions (Fig. 2A). Whereas the relatively long time frame shown extends over a number of successive stimuli, response averaging is time-locked to visual stimuli presented at time zero; because of the jitter in SOA, responses to prior and succeeding stimuli (red and blue brackets) appear "smeared" in the CSD plot. Along with a clear attentional enhancement of the visual response, a noteworthy pattern of underlying oscillatory entrainment is also evident. At the time of stimulus presentation (dotted line), supragranular baseline CSD activity (along with activity in the infragranular layers) is opposite in sign in the AV and AA conditions, whereas the sign of granular-layer prestimulus CSD activity is the same for each condition (this pattern was consistent across sessions) (fig. S2). Overlay of the CSD waveforms from the selected supragranular electrode "S" (Fig. 2B) shows that the baseline effect is not a result of a direct current shift in excitability; instead it is a cyclical delta-band oscillation with a period matching the rate of visual stimulation, which is 180 degrees out of phase in the AV and AA conditions. Supragranular entrainment by attention is confirmed by the single-trial delta-phase distribution at 1.55 Hz (visual stimulation frequency) (Fig. 2C) and mean delta phase at visual stimulus onset across all experiments (Fig. 2D). Whereas delta phase at visual stimulus onset was close to the negative peak (ϕ mean = 2.7 rad, ϕ dev = 0.61, n = 24 experiments) in the AV condition, it was in the opposite phase around the positive peak (ϕ mean = 0.23 rad, ϕ dev = 0.87, n = 24) in the AA condition. Because of entrainment, the delta-phase distribution was significantly biased (i.e., nonrandom) in both conditions in all experiments (Rayleigh's uniformity tests, $P < 0.01$). However, intertrial coherence values—indexing phase similarity across trials—were always larger for relevant versus irrelevant stimuli (*12*), independent of modality (supporting online material), which indicates that phase alignment/entrainment is controlled by attention. The fact that oscillations in V1 entrain to attended auditory stimuli just as well as to attended visual stimuli reinforces the view that the primary cortices are not the exclusive domain of a single-input system (*20*) and confirms the role of attention in modulating the impact of heteromodal stimuli in the primary cortical regions (*21*, *22*).

In both monkeys (*3*) and humans (*6*), neuronal oscillations in the neocortex tend to couple hierarchically, with the phase of lower-frequency oscillations modulating the amplitudes of higher-frequency ones. Excitability is also coupled to oscillatory phase [prediction (ii)] (*1*–*3*). These related types of coupling are both observed in the present results. Time-frequency plots (Fig. 2E, left and right) and spectrograms (Fig. 2E, middle) computed for the supragranular site (S) in the AV and AA conditions show that the amplitude of oscillations above 4 Hz (including activity in both the theta and gamma bands) is modulated in counterphase in the two attention conditions, at the period of the entrained delta oscillation (Fig. 2F). As a consequence of their coupling to delta oscillations, these higher-frequency oscillations display increasing amplitude near visual stimulus onset in the AV condition but decreasing amplitude near visual stimulus onset in the AA condition. This "countersign modulation" of prestimulus gamma oscillations was present in all 24 experimental sessions, and the same was true for the prestimulus MUA (Fig. 2G). Gamma amplitude and MUA, which have both been linked to excitability previously (*8*, *23*–*25*), are thus larger in the AV condition around the time of visual stimulus onset, smaller around the time of auditory stimulus onset, and vice versa in the AA condition.

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The above findings suggest that delta-band entrainment can account for the large visual-response amplitude difference in the two attention conditions [prediction (iii)]. To verify this, we measured the influence of prestimulus delta phase on single-trial event-related responses. Figure 3A shows visual event-related laminar CSD amplitude and MUA profiles from an additional experiment, with a typical attention-related response amplitude difference. Figure 3B shows that the single-trial amplitude of the visual response is systematically related to the phase of prestimulus delta oscillation in both attention conditions. Moreover, because amplitudes are measured from signals that are baseline corrected to the immediate prestimulus period, the enhancement reflects modulation of response gain, rather than superposition of an unmodulated response on a modulated background signal. In all of our experiments, the largest CSD and MUA amplitudes occur around the negative peak (high-excitability phase), whereas the smallest response amplitudes occur around the positive peak (low-excitability phase) of delta oscillations. Given this dependence of response amplitude on delta phase (Fig. 3B), the strong counterphase entrainment of delta oscillation in the AV and AA conditions (Fig. 3D) can account for most of the attentional modulation of the visual-response amplitude. As in Fig. 3B, there is an amplitude offset between the AV and AA functions in most of our experiments, indicating larger response amplitudes for attended versus nonattended visual stimuli with the same prestim-

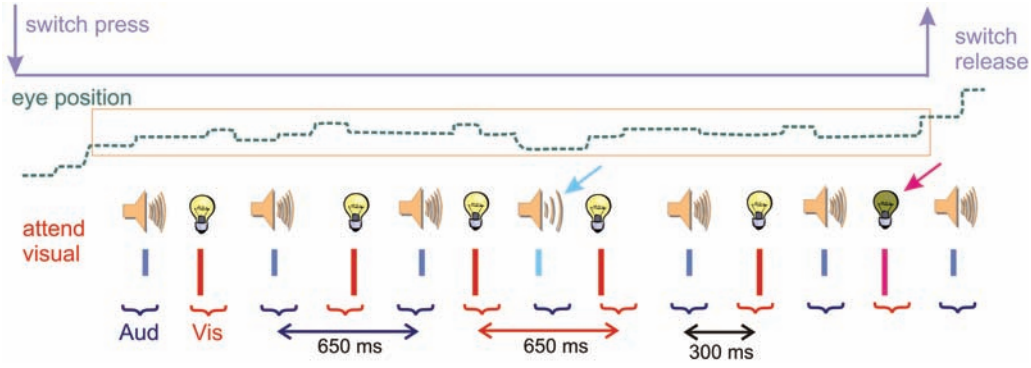

Fig. 1. Intermodal selective-attention task. Light bulbs and speakers represent visual and auditory stimuli in the mixed stimulus stream. Visual and auditory deviants are marked by light blue and magenta arrows, respectively. Stimulation began when the monkey depressed a switch and maintained a gaze (dashed line) within an eye position "window" (orange box). SOA within modality was jittered (Gaussian distribution) around a mean of 650 ms. SOA between modalities was 300 ms, on average.

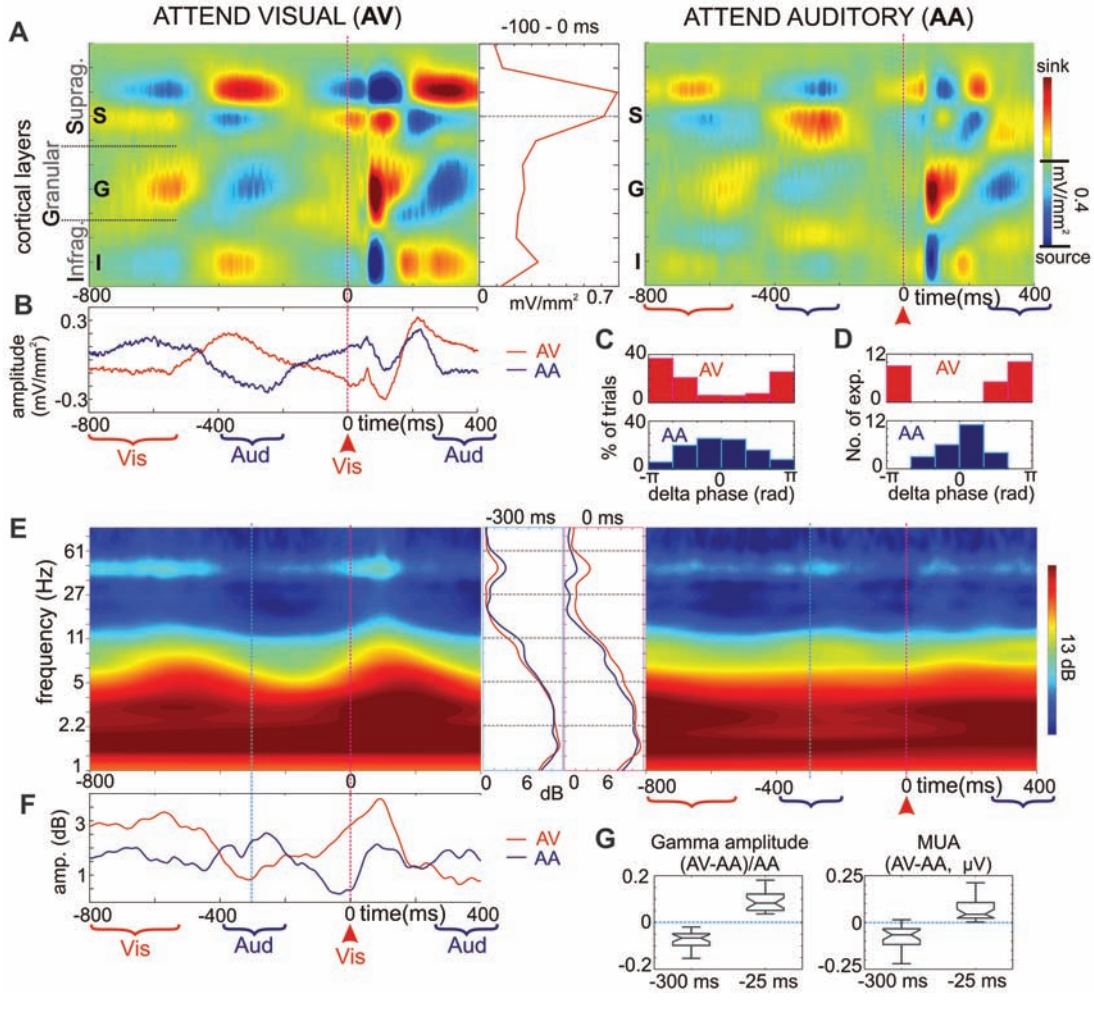

Fig. 2. Entrainment and the oscillatory hierarchy. (**A**) Color maps show CSD profiles related to standard visual stimuli in the AV and AA conditions for the −800 to +400 ms time frame from a representative experiment. Traces between the CSD maps show the laminar profile of prestimulus oscillation amplitude based on the Hilbert transform of the CSD (−100 to 0 ms). The red arrowhead indicates the visual event used as trigger (0 ms). Blue and red brackets indicate the time frames in which adjoining auditory and visual events occur, respectively. (**B**) CSD from supragranular electrode "S" in the AV and AA conditions. (**C**) Distribution of single-trial supragranular prestimulus (0 ms) delta oscillatory phases in the same experiment. (**D**) Pooled prestimulus mean (across trials) delta phase for all experiments (n = 24). (**E**) Time-frequency plots display the average oscillatory amplitude of the wavelet-transformed single trials in the selected supragranular site in (A). Traces in the middle show prestimulus amplitude spectra in the AV and AA conditions at −300 and 0 ms. (**F**) Time courses of the averaged (37 to 57 Hz) gamma amplitudes. (**G**) Pooled (n = 24) normalized gamma-amplitude and MUA differences between AV and AA conditions [(AV-AA)/AA)] for the −325 to −275 and −50 to 0 ms time frames. Notches in the boxes indicate a 95% confidence interval about the median of each distribution. Whiskers extend to the most extreme values.

ulus delta phase. This offset suggests that there may be some attentional modulation independent of local delta entrainment (Fig. 3C).

Enhanced prestimulus neuronal gamma-band synchronization (amplitude) in V4 is related to shorter reaction times (*23*). Because delta phase controls gamma amplitude (Fig. 2F) (*3*), it should also affect reaction time [prediction (iv)]. Figure 4 shows a systematic relation between delta phase at the time of visual target onset (0 ms) and reaction time. For each experiment, we then determined the 25% of trials with the fastest (orange arrow) and slowest (green arrow) reaction times and the corresponding mean delta phases. These two groups of trials were not overlapping in any of the 24 experiments. We found the fastest reaction times around the negative peak of prestimulus delta oscillations (ϕ mean = 2.96 rad, ϕ dev = 0.49, n = 24), whereas the slowest group was always around the positive peak (ϕ mean = 0.44 rad, ϕ dev = 0.53, n = 24), as shown in Fig. 4B. Reaction times were significantly different for the "fast" and "slow" 25% of trials in all 24 cases (Wilcoxon rank sum, $P < 0.05$); on average, they were 14.3% (SD = 7) faster in the fast group. Thus, there is a strong relation between prestimulus delta phase and reaction time.

Overall, our findings suggest that when the brain can detect a rhythm in a task, attention enforces phase resetting and entrainment of neuronal excitability oscillations to the relevant stimulus stream, thus changing response gain and amplifying neuronal responses to the events in that stream. A similar predictive effect operating with single-trial cuing may underlie "orienting of attention in time" (*26*). An associated event-related potential effect, the "contingent negative variation" (*27*), may reflect a low-frequency frontal cortical oscillation, reset by a warning cue. Whereas slow excitability oscillations can be useful when stimulus timing is predictable, their cost is "downtime," and random inputs arriving during extended low-excitability phases are less likely to be detected, as in the case of an "inhibition of return" (*28*). Thus, when the brain cannot detect a rhythm in stimulus occurrence, a continuous processing mode is initiated, and low-frequency oscillations are suppressed (*8*). Rhythmic processing is not uniquely linked to delta oscillations because oscillations in numerous frequency ranges can entrain to rhythmic stimulation (*3*, *12*–*16*). Although earlier studies suggest that the entrained oscillations we report may represent spontaneously occurring neural oscillations aligned by phase resetting to the structure of attended stimulus streams (*3*, *20*), we

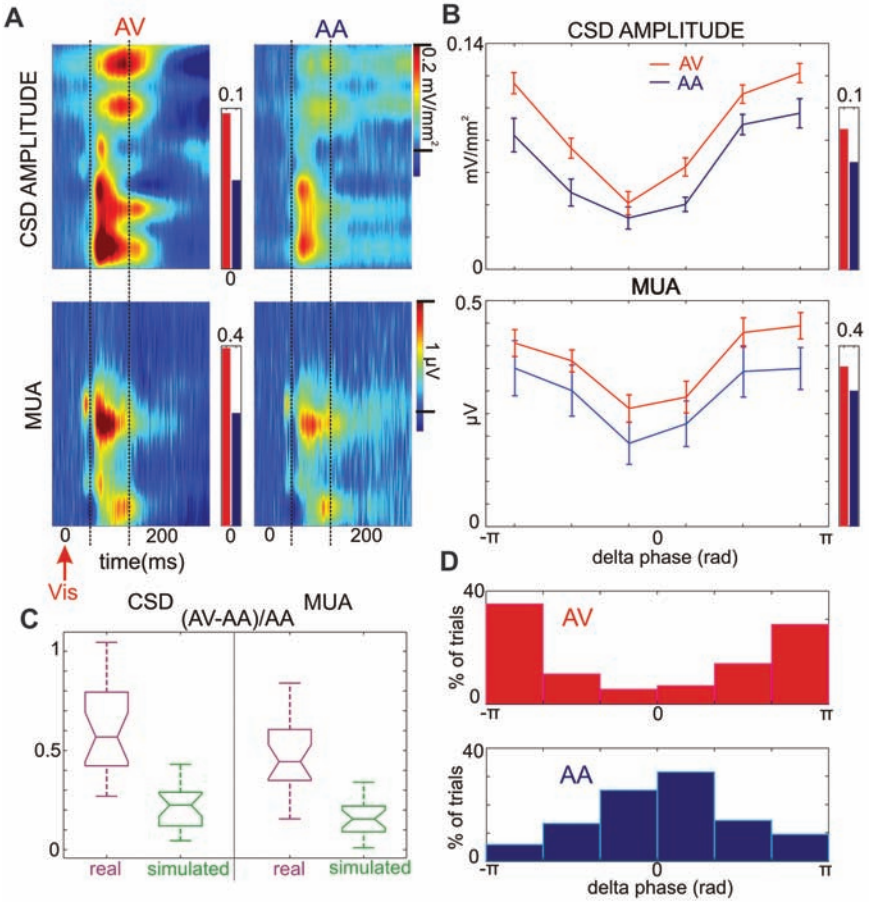

Fig. 3. Prestimulus delta phase and its effect on the visual event-related response. (**A**) Laminar CSD (top) and MUA (bottom) profiles elicited by standard visual stimuli in a representative experiment. Red and blue bars between the color maps represent response amplitudes for the 50 to 135 ms time interval in the AV and AA conditions, respectively ("real" average). (**B**) Response amplitudes sorted into six bins on the basis of prestimulus delta phase. Red and blue bars at right represent response amplitudes averaged across the bins using the mean of each bin ("simulated" average). Error bars indicate SE. (**C**) Pooled (n = 24) normalized CSD and MUA response amplitude differences between AV and AA conditions [(AV-AA)/AA)] for real and simulated averages [see (A) and (B)]. Notches in the boxes indicate a 95% confidence interval about the median. Whiskers extend to the most extreme values. (**D**) Distribution of single-trial supragranular prestimulus (0 ms) delta phases in the same experiment.

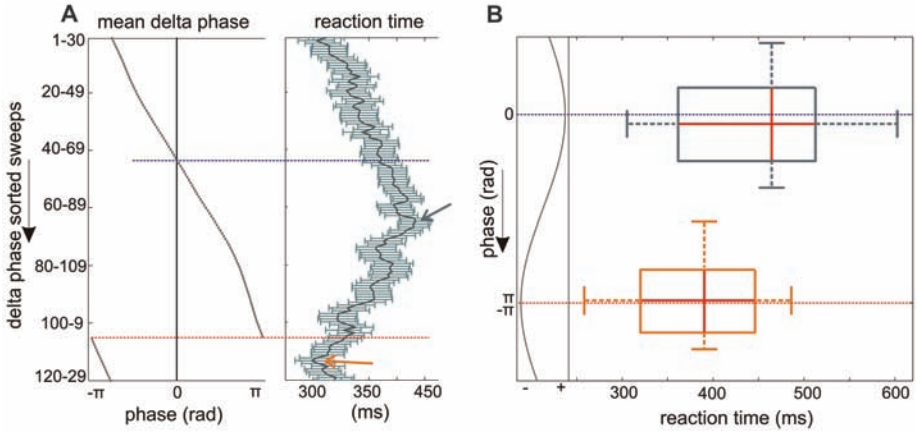

Fig. 4. Delta phase and reaction time. (**A**) Deviant trials with correct responses were sorted on the basis of delta phase at 0 ms from $-\pi$ to π rad on the selected supragranular electrode in a representative experiment. After sorting, we calculated the mean phase (left) and mean reaction time (green line on the right; error bars denote SE) in groups of trials corresponding to 25% of all trials starting with each consecutive trial. Blue and red dotted lines denote the groups of trials corresponding to the positive and negative peak of prestimulus delta oscillation. Green and orange arrows point to groups with the slowest and fastest reaction times, respectively. (**B**) Two-dimensional box plots show pooled mean reaction time (x axis) and pooled mean prestimulus delta phase (y axis) for all experiments (n = 24). Red lines in the boxes denote the medians, whereas boxes extend to the lower- and upper-quartile values. Whiskers extend to the most extreme values.

cannot yet differentiate this account from alternative interpretations.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/320/5872/110/DC1
Materials and Methods
Figs. S1 and S2
References

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Episodic-Like Memory in Rats: Is It Based on When or How Long Ago?

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Recent experiments with rats suggest that they show episodic-like or what-where-when memory for a preferred food found on a radial maze. Although memory for when a salient event occurred suggests that rats can mentally travel in time to a moment in the past, an alternative possibility is that they remember how long ago the food was found. Three groups of rats were tested for memory of previously encountered food. The different groups could use only the cues of when, how long ago, or when + how long ago. Only the cue of how long ago food was encountered was used successfully. These results suggest that episodic-like memory in rats is qualitatively different from human episodic memory.

Although Tulving (*1*) initially defined episodic memory as a person's ability to remember a personal past event (what) including where and when it happened, he later amended this definition to include autonoetic consciousness or the feeling of retrieving a personal episode (*2*). It was argued further that episodic memory is found only in humans (*3*). However, recent research with birds and rodents has brought this position into question. By using Tulving's original criteria of what-where-when, it has been shown in behavioral experiments that scrub jays (*4*–*6*) and rats (*7*–*10*) remember where and when they cached or discovered foods of differing palatability. Because these experiments could not involve an assessment of autonoetic consciousness, their findings have been taken as evidence for episodic-like memory, a form of memory in animals that may have some of the properties of human episodic memory (*11*).

Of particular importance in these studies was the discovery that animals could remember when they had cached or encountered a favored food. Memory for when suggests that animals can mentally travel in time or locate a past event within a temporal framework of hours and days (*12*). An alternative possibility is that, instead of remembering when an event happened within a framework of past time, animals are keeping track of how much time has elapsed since caching or encountering a particular food item at a particular place and are using elapsed time to indicate return to or avoidance of that location (*12*). The cues of when and how long ago are typically confounded in studies of episodic-like memory. Thus, animals might be remembering how long ago an event occurred by keeping track of elapsed time using accumulators, circadian timers, their own behavior, or the strength of a decaying memory trace (*13*–*17*). If this is the case, then episodic-like memory in animals may be quite different from human episodic memory in which people can reconstruct past experiences within an absolute temporal dimension (*18*–*20*).

In two experiments, we asked whether the temporal cues used by rats to show episodic-like memory were when the study phase occurred, how long ago it occurred, or whether rats needed both when and how long ago cues. Three groups of 10 Long-Evans hooded rats each were tested (*21*), in one procedure in which the cue of when was relevant and the cue of how long ago was made irrelevant, a second in which how long ago was relevant and when was irrelevant, and a third in which rats could use when + how long ago (Fig. 1). Within daily trials, rats were allowed to enter four randomly chosen arms of an eight-arm radial maze during a study phase that could occur at 9 a.m. or 12:30 p.m. Three of the arms contained two Noyes 45-mg reward pellets, and the fourth arm contained the highly preferred reward of a cube of cheese (*10*). The rats were returned to the maze for a test phase at 9:30 a.m., 1 p.m., or 4:30 p.m. On the test phase, all eight arms were open, and rats could choose freely among them. The four arms closed during the study phase now contained two reward pellets, and the three arms that contained pellets during the study phase were empty.

Groups When and How Long Ago (HLA) had study phase trials at either 9 a.m. or 12:30 p.m. and test phase trials at 9:30 a.m., 1 p.m., or 4:30 p.m. (Fig. 1). On the arm where a rat consumed cheese in the study phase, another piece of cheese was placed on the same arm to replenish (R) it or the arm was empty, as the cheese had been pilfered (P); these conditions were found at different times for subgroups A and B within each group. Notice that the When group always had the cheese arm replenished after entering it at 9 a.m. (subgroup B) or at 12:30 p.m. (subgroup A) and pilfered after entering it at 12:30 p.m. (subgroup B) or at 9 a.m. (subgroup A). These rats then could only consistently return to the replenished cheese arm early on the appropriate trials if they used "when" as a cue and not how long ago the cheese arm had been encountered. The opposite arrangement was in effect for rats in the HLA group; subgroups A and B always had the cheese arm replenished after 30 min or 4 hours, and when the rats first encountered the cheese arm was made irrelevant. Rats in the When + HLA condition were tested under a standard procedure (*10*) in which both the time of the study phase and the interval until testing could indicate whether the

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