10. Y. Sato, T. Hirata, M. Ogawa, H. Fujisawa, *J. Neurosci.* **18**, 7800 (1998).
11. T. Hirata, H. Fujisawa, *J. Neurobiol.* **38**, 93 (1999).
12. A. Kawakami, T. Kitsukawa, S. Takagi, H. Fujisawa, *J. Neurobiol.* **29**, 1 (1996).
13. E. Steck *et al.*, *Biochem. J.* **353**, 169 (2001).
14. E. Steck *et al.*, *Matrix Biol.* **26**, 30 (2007).
15. J. C. Loftus, J. W. Smith, M. H. Ginsberg, *J. Biol. Chem.* **269**, 25235 (1994).
16. T. Hirokawa, S. Boon-Chieng, S. Mitaku, *Bioinformatics* **14**, 378 (1998).
17. A. E. Fournier, T. GrandPre, S. M. Strittmatter, *Nature* **409**, 341 (2001).
18. B. P. Liu, A. Fournier, T. GrandPré, S. M. Strittmatter, *Science* **297**, 1190 (2002); 10.1126/science1073031.
19. B. P. Liu, W. B. Cafferty, S. O. Budel, S. M. Strittmatter, *Philos. Trans. R. Soc. London Ser. B* **361**, 1593 (2006).
20. G. Yiu, Z. He, *Nat. Rev. Neurosci.* **7**, 617 (2006).
21. H. Tozaki, T. Kawasaki, Y. Takagi, T. Hirata, *Brain Res. Mol. Brain Res.* **104**, 111 (2002).
22. T. GrandPré, F. Nakamura, T. Vartanian, S. M. Strittmatter, *Nature* **403**, 439 (2000).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/333/6043/769/DC1
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Figs. S1 to S15
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Integrating What and When Across the Primate Medial Temporal Lobe

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Episodic memory or memory for the detailed events in our lives is critically dependent on structures of the medial temporal lobe (MTL). A fundamental component of episodic memory is memory for the temporal order of items within an episode. To understand the contribution of individual MTL structures to temporal-order memory, we recorded single-unit activity and local field potential from three MTL areas (hippocampus and entorhinal and perirhinal cortex) and visual area TE as monkeys performed a temporal-order memory task. Hippocampus provided incremental timing signals from one item presentation to the next, whereas perirhinal cortex signaled the conjunction of items and their relative temporal order. Thus, perirhinal cortex appeared to integrate timing information from hippocampus with item information from visual sensory area TE.

Episodic memory, or the ability to mentally reexperience a previous event in one's life, is formed when individual events or items become bound to the specific temporal context in which the event took place (*1*, *2*). The human medial temporal lobe (MTL) is critical for episodic memory presumably because of its role in binding individual stimuli or events to their temporal and spatial contexts (*3*–*5*). Computation models (*6*, *7*) have proposed that cortical association areas signal information about items, parahippocampal regions signal information about items along with their temporal context, whereas hippocampus (HPC) supervises these item-context associations. Consistent with these model predictions, functional magnetic resonance imaging (fMRI) studies in humans report both HPC and parahippocampal activation during tasks of temporal-order memory (*8*, *9*). Recent neurophysiological studies in the rodent have highlighted the role of HPC in signaling either a particular time within a trial (*10*, *11*) or incremental timing across the entire recording session (*12*). However, little is known about the neurophysiological basis of how item and timing information is integrated within MTL. We therefore recorded neural activity from MTL areas and a control visual area (fig. S1) (*13*–*16*) as nonhuman primates performed a temporal-order memory task (*17*, *18*) that required encoding of two visual items and their temporal order (Fig. 1, A and B) (*19*).

A total of 644 neurons were recorded in the two macaques (table S1). We evaluated the effects of "time" and "item" on the cue responses separately for each neuron. We referred to neurons whose responses differentiated between the cue 1 and cue 2 periods on a two-tailed paired *t* test ($P < 0.01$) as "time cells" that could signal relative timing between cue presentations or temporal order of cue presentations. The neurons that showed significant stimulus-selective activity during either cue 1 or cue 2 on a one-way analysis of variance with the eight stimuli as a main factor ($P < 0.005$ for each cue) were referred to as "item cells." Numbers of these task-related neurons (time or item cells) were significantly greater than expected by chance (~2% of the recorded neurons) in all areas [53/193, HPC; 29/143, entorhinal cortex (ERC); 68/231, perirhinal cortex (PRC); 50/77 TE; $P < 0.0001$ for each area, χ^2 test]. We compared the proportions of time and item cells across areas and found the highest proportions of item cells in visual area TE, with gradually decreasing proportions seen in PRC, ERC, and HPC (Fig. 1C, open bars). In contrast, we observed the highest proportions of time cells in HPC (solid bars). The proportions of time cells and item cells were significantly different across areas ($P < 0.0001$, χ^2 test). These results suggest the possibility that

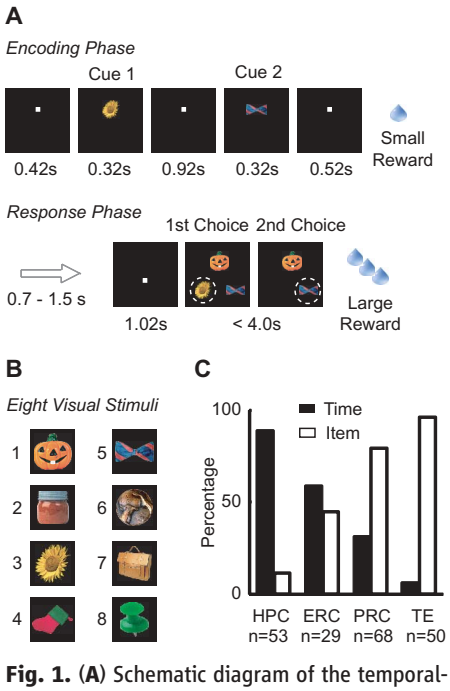

Fig. 1. (**A**) Schematic diagram of the temporal-order task. A sequence of two cue stimuli was presented in the encoding phase. The two cue items and one distracter were presented at three different positions randomly in the response phase. Dashed circles indicate correct targets. (**B**) The eight visual stimuli used in the task. (**C**) Relative proportions of time cells and item cells in each area.

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time information flows from HPC to ERC and PRC, whereas item information flows from TE to PRC and ERC.

We first examined the prominent time signals in HPC. Figure 2A shows an example of a typical time cell in HPC that showed stronger responses during cue 2 relative to cue 1. This cell started to respond in the middle of the delay period between cue 1 and cue 2 (i.e., cue 1 delay period) and continued firing strongly during cue 2. We also observed HPC time cells with high firing rates during cue 1 that decreased their activity substantially during the cue 1 delay period (Fig. 2B). This characteristic timing signal was also seen at the level of the local field potential (LFP). HPC started to increase its gamma band activity (>30 Hz) during the cue 1 delay period (Fig. 3A), and the gamma band activity in HPC was significantly stronger during cue 2 than cue 1 ($P < 0.0001$, two-tailed paired t test) (table S3). No such difference was observed in the other three areas (Fig. 3, B to D).

To characterize the temporal dynamics of time cells observed throughout the MTL, we applied a population vector analysis (*12*, *20*). We constructed n-dimensional vectors from the responses of time cells for 40-ms time bins throughout the cue 1 delay period, where "n" is the number of time cells in each area (*19*). In HPC, the distance of this vector from a "template" defined as the cue 1 state increased at a constant rate during the cue 1 delay period (Fig. 2C, solid circles) as evaluated by a polynomial curve fitting approach (table S4), whereas the distance to the cue 2 state (open squares) decreased at a constant rate. This pattern of activity was confirmed in both animals (fig. S3). These results indicated that, as a population, HPC time cells provide an incremental timing signal that gives an estimate of the relative time from the last cue presentation as well as an estimate of the relative time to the next cue presentation (fig. S7B). An incremental timing signal was not present in PRC, where there was a more sudden shift in the distance measures from both the cue 1 and cue 2 states early in the cue 1 delay period that then remained relatively constant for the remainder of the delay period (Fig. 2E). ERC appeared to exhibit an intermediate pattern such that the distance measures from the cue 1 state changed in a gradual manner but the distance to the cue 2 state did not (Fig. 2D). Principal component analysis of neuronal activity during the encoding phase also supported the idea of a strong incremental timing signal in HPC and a similar but weaker such signal in ERC (fig. S4). To determine which area provided the most accurate representation of the cue 2 state before the presentation of cue 2, we asked which of the three areas exhibited the shortest distance to the cue 2 state during the last quarter (240 ms) of the cue 1 delay period. We found that HPC exhibited the shortest distance to cue 2 (Fig. 2F).

We next examined the information carried by item cells in TE, PRC, and ERC. We first asked whether item cells represented the same

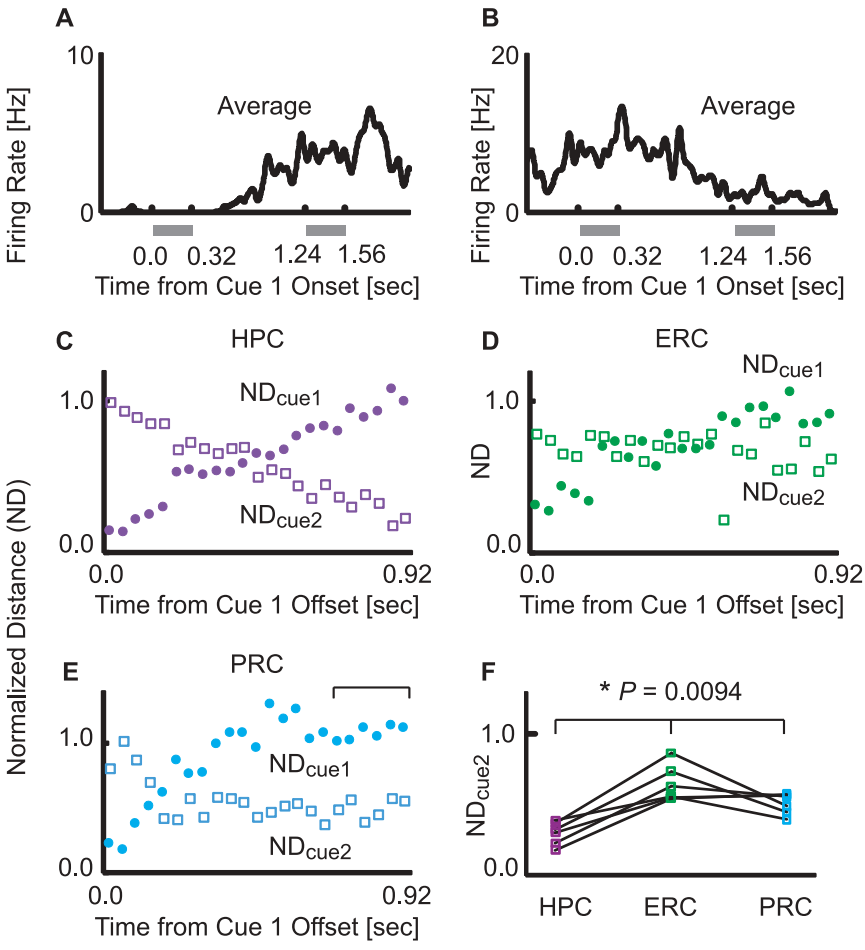

Fig. 2. (**A**) An example of an HPC time cell showing greater responses during cue 2 than cue 1. Shown is the average spike density function (SDF, σ = 20 ms) across all trials in the encoding phase. (**B**) An example of an HPC time cell showing greater responses during cue 1 than cue 2. (**C** to **E**) Normalized distances (NDs) from the cue 1 states (solid circles) and the cue 2 states (open squares) in each area. (**F**) Comparison of NDs to the cue 2 states during the last 240 ms (six bins) of the cue 1 delay period. The values at the same time points are connected by lines. The NDs were significantly different in the three areas (Friedman test).

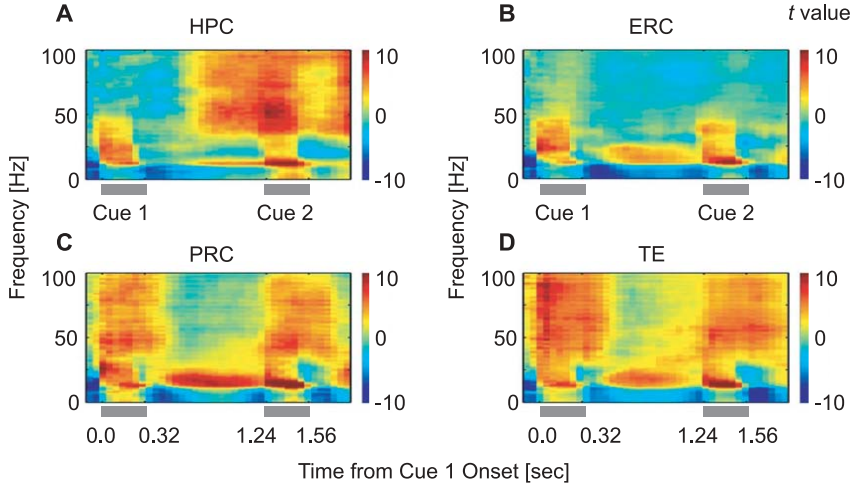

Fig. 3. (**A** to **D**) Two-dimensional plots of the population average LFP spectrogram in HPC ($n = 62$), ERC ($n = 54$), PRC ($n = 49$), and TE ($n = 29$). Time is on x axis; frequency is on y axis. Red pixels indicate time-frequency domains in which activity was stronger than that in control period (pixels centered on 150 ms and 100 ms before cue 1 onset). Blue pixels indicate the opposite pattern. The differential activities were evaluated by t values (paired t test).

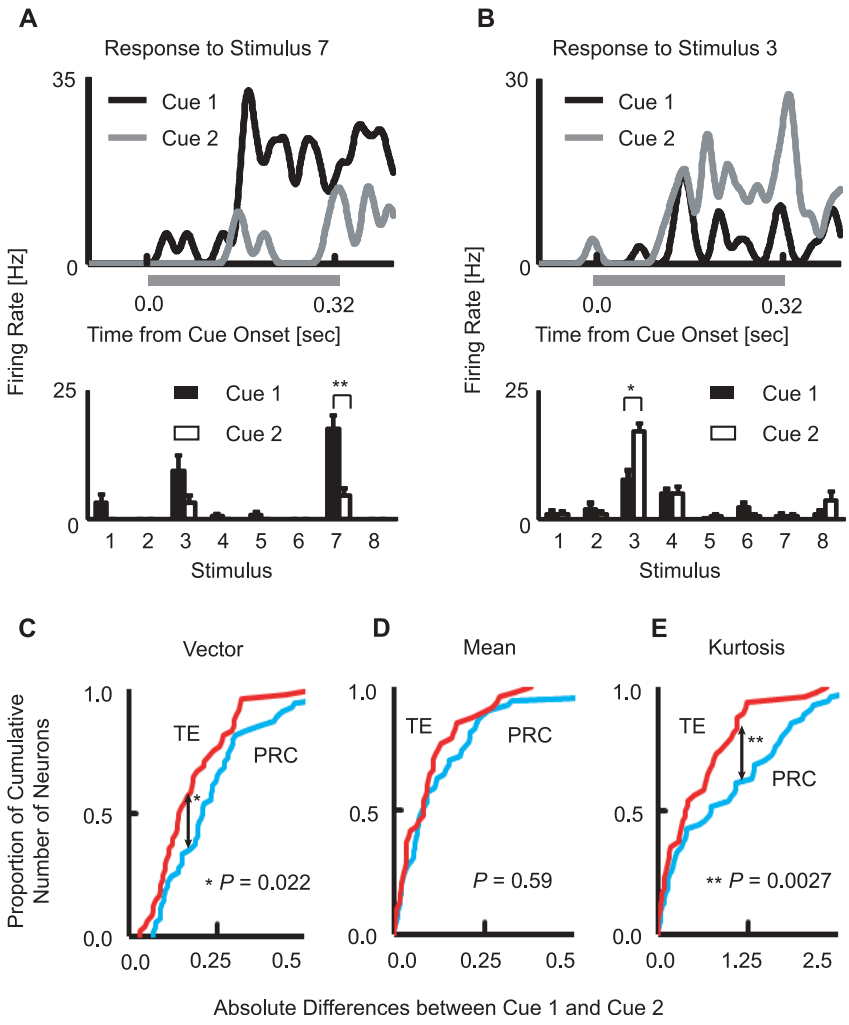

Fig. 4. (**A**) An example of a PRC item cell. (Top) SDFs to stimulus 7 for cue 1 superimposed with cue 2. (Bottom) Mean discharge rates and SEM during cue 1 and cue 2. Double asterisk, significantly different responses between cue 1 and cue 2 ($P = 0.002$, two-tailed t test). (**B**) Another example of a PRC item cell. (Top) SDFs to stimulus 3. (Bottom) The same formats as (A). Asterisk, $P = 0.012$. (**C**) Cumulative frequency histograms of normalized vector distances between cue 1 and cue 2 for PRC ($n = 54$; light blue) and TE ($n = 48$; red). (**D** and **E**) The same formats as (C) but for absolute differences of normalized mean discharge rates and kurtosis, respectively.

items across the two cue periods. To address this question, we analyzed the correlation coefficient between response amplitudes of all eight stimuli during cue 1 and cue 2 (*21*). The correlation coefficients in ERC (median = 0.62) were significantly smaller than either PRC (median = 0.86; $P = 0.0077$, Kolmogorov-Smirnov test) or TE (median = 0.90; $P = 0.0017$). The small correlation coefficients in ERC can be explained by the lack of stimulus selectivity in one of the two cue periods (fig. S5). This differential level of stimulus selectivity between cue periods can serve to integrate item information with a relative timing signal [supporting online material (SOM) text]. In contrast, PRC and TE represented the same items across the two cue periods. Closer examination of these responses revealed a time effect in PRC such that the response to the neuron's preferred stimulus differed across cue 1 and cue 2 (Fig. 4, A and B). This temporal modulation for preferred items was observed for the entire population of PRC item cells (fig. S6A), suggesting that these cells may integrate item and temporal order information by modulating their stimulus-selective response properties across the cue periods.

To test this hypothesis, we defined two vectors consisting of the response amplitudes to the eight stimuli presented during cue 1 or cue 2. The distance between the two vectors was normalized by the sum of the two vectors' lengths. The normalized distances were significantly greater for item cells in PRC compared with those in TE (Fig. 4C, $P = 0.022$, Kolmogorov-Smirnov test), suggesting a more prominent time effect in PRC. This differential time effect between PRC and TE could be explained either by general increases or decreases in firing rates or by changes in tuning curve sharpness across the two cue periods. When we compared the mean responses to all eight stimuli between the two cue periods, we found no differential time effect between the two areas (Fig. 4D, $P = 0.59$). By contrast, when we examined the sharpness of the tuning curve during the two cue periods using a kurtosis measure (*21*, *22*), we found the absolute difference of the measures between the two cue periods was significantly greater in PRC compared with TE (Fig. 4E, $P = 0.0027$). This suggests that PRC differentiates between the cue 1 and cue 2 periods by changing the sharpness of its stimulus-selective response.

The present study provides insight about how individual MTL structures may integrate item and timing information (i.e., "what" and "when") in the service of episodic memory (*6*–*9*) (fig. S7). HPC provides a robust incremental timing signal (*10*–*12*) that may serve to anchor the timing to events within an episode (*23*). Consistent with predictions from previous computational models (*6*, *7*), our data show that PRC neurons integrate time and item information by modulating their stimulus-selective response properties across temporally distinct stimulus presentations. ERC neurons can signal incremental timing information as well as integrate item and time information, albeit at a lower magnitude than HPC or PRC, respectively. We hypothesize that the incremental timing signal in HPC is conveyed to PRC via ERC, where it is integrated with item information from TE and converted into a discrete item-based temporal order signal.

References and Notes

1. H. Eichenbaum, N. Fortin, *Curr. Dir. Psychol. Sci.* **12**, 53 (2003).
2. E. Tulving, *Annu. Rev. Psychol.* **53**, 1 (2002).
3. J. J. Downes, A. R. Mayes, C. MacDonald, N. M. Hunkin, *Neuropsychologia* **40**, 853 (2002).
4. F. Vargha-Khadem *et al.*, *Science* **277**, 376 (1997).
5. M. Moscovitch, L. Nadel, G. Winocur, A. Gilboa, R. S. Rosenbaum, *Curr. Opin. Neurobiol.* **16**, 179 (2006).
6. M. W. Howard, M. J. Kahana, *J. Math. Psychol.* **46**, 269 (2002).
7. M. W. Howard, M. S. Fotedar, A. V. Datey, M. E. Hasselmo, *Psychol. Rev.* **112**, 75 (2005).
8. L. J. Jenkins, C. Ranganath, *J. Neurosci.* **30**, 15558 (2010).
9. S. Tubridy, L. Davachi, *Cereb. Cortex* **21**, 272 (2011).
10. E. Pastalkova, V. Itskov, A. Amarasingham, G. Buzsáki, *Science* **321**, 1322 (2008).
11. P. R. Gill, S. J. Mizumori, D. M. Smith, *Hippocampus* 10.1002/hipo.20832 (2010).
12. J. R. Manns, M. W. Howard, H. Eichenbaum, *Neuron* **56**, 530 (2007).
13. W. A. Suzuki, D. G. Amaral, *J. Comp. Neurol.* **350**, 497 (1994).
14. Y. Naya, M. Yoshida, Y. Miyashita, *Science* **291**, 661 (2001).
15. S. Wirth *et al.*, *Science* **300**, 1578 (2003).
16. K. Tanaka, *Annu. Rev. Neurosci.* **19**, 109 (1996).
17. Y. Ninokura, H. Mushiake, J. Tanji, *J. Neurophysiol.* **89**, 2868 (2003).
18. M. R. Warden, E. K. Miller, *Cereb. Cortex* **17** (suppl. 1), i41 (2007).
19. Information on materials and methods are available on *Science* Online.
20. O. Barak, M. Tsodyks, R. Romo, *J. Neurosci.* **30**, 9424 (2010).
21. Y. Naya, M. Yoshida, Y. Miyashita, *J. Neurosci.* **23**, 2861 (2003).
22. S. R. Lehky, T. J. Sejnowski, R. Desimone, *Vision Res.* **45**, 57 (2005).
23. R. Paz *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **107**, 6046 (2010).

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Supporting Online Material
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Google Effects on Memory: Cognitive Consequences of Having Information at Our Fingertips

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The advent of the Internet, with sophisticated algorithmic search engines, has made accessing information as easy as lifting a finger. No longer do we have to make costly efforts to find the things we want. We can "Google" the old classmate, find articles online, or look up the actor who was on the tip of our tongue. The results of four studies suggest that when faced with difficult questions, people are primed to think about computers and that when people expect to have future access to information, they have lower rates of recall of the information itself and enhanced recall instead for where to access it. The Internet has become a primary form of external or transactive memory, where information is stored collectively outside ourselves.

In a development that would have seemed extraordinary just over a decade ago, many of us have constant access to information. If we need to find out the score of a ball game, learn how to perform a complicated statistical test, or simply remember the name of the actress in the classic movie we are viewing, we need only turn to our laptops, tablets, or smartphones and we can find the answers immediately. It has become so commonplace to look up the answer to any question the moment it occurs that it can feel like going through withdrawal when we can't find out something immediately. We are seldom offline unless by choice, and it is hard to remember how we found information before the Internet became a ubiquitous presence in our lives. The Internet, with its search engines such as Google and databases such as IMDB and the information stored there, has become an external memory source that we can access at any time.

Storing information externally is nothing particularly novel, even before the advent of computers. In any long-term relationship, a team work environment, or other ongoing group, people typically develop a group or transactive memory (*1*), a combination of memory stores held directly by individuals and the memory stores they can access because they know someone who knows that information. Like linked computers that can address each other's memories, people in dyads or groups form transactive memory systems (*2*, *3*). The present research explores whether having online access to search engines, databases, and the like, has become a primary transactive memory source in itself. We investigate whether the Internet has become an external memory system that is primed by the need to acquire information. If asked the question whether there are any countries with only one color in their flag, for example, do we think about flags or immediately think to go online to find out? Our research then tested whether, once information has been accessed, our internal encoding is increased for where the information is to be found rather than for the information itself.

In experiment 1, participants were tested in two within-subject conditions (*4*). Participants answered either easy or hard yes/no trivia questions in two blocks. Each block was followed by a modified Stroop task (a color-naming task with words presented in either blue or red) to test reaction times to matched computer and noncomputer terms (including general and brand names for both word groups). People who have been disposed to think about a certain topic typically show slowed reaction times (RTs) for naming the color of the word when the word itself is of interest and is more accessible, because the word captures attention and interferes with the fastest possible color naming.

Paired within-subject t tests were conducted on color-naming reaction times to computer and general words after the easy and difficult question blocks. Confirming our hypothesis, computer words were more accessible [color-naming RT mean (M) = 712 ms, SD = 413 ms] than general words (M = 591 ms, SD = 204 ms) after participants had encountered a series of questions to which they did not know the answers, $t(68) = 3.26$, $P < 0.003$, two-tailed. It seems that when we are faced with a gap in our knowledge, we are primed to turn to the computer to rectify the situation. Computer terms also interfered somewhat more with color naming (M = 603 ms, SD = 193 ms) than general terms (M = 559 ms, SD = 182 ms) after easy questions, t (68) = 2.98, $P < 0.005$, suggesting that the computer may be primed when the concept of knowledge in general is activated.

Comparison using a repeated measures analysis of variance (ANOVA) of specific search engines (Google/Yahoo) and general consumer-good brand names (Target/Nike) revealed an interaction with easy versus hard question blocks, $F(1,66) = 5.02$, $P < 0.03$, such that search engine brands after both easy questions (M = 638 ms, SD = 260 ms) and hard questions (M = 818 ms, SD = 517 ms) created more interference than general brands after easy questions (M = 584 ms, SD = 220 ms) and hard questions (M = 614 ms, SD = 226 ms) (Fig. 1). Simple effects tests showed that the interaction was driven by a significant increase in RT for the two search engine terms after the hard question block, $F(1,66) = 4.44$, $P < 0.04$ (Fig. 1). Although the concept of knowledge in general seems to prime thoughts of computers, even when answers are known, not knowing the answer to general-knowledge questions primes the need to search for the answer, and subsequently computer interference is particularly acute.

In experiment 2, we tested whether people remembered information that they expected to have later access to—as they might with information they could look up online (*4*). Participants were tested in a 2 by 2 between-subject experiment by reading 40 memorable trivia statements of the type that one would look up online (both of the new information variety, e.g., "An ostrich's eye is bigger than its brain," and information that may be remembered generally, but not in specific detail, e.g., "The space shuttle Columbia disintegrated during re-entry over Texas in Feb. 2003."). They then typed them into the computer to ensure attention (and also to provide a more generous test of memory). Half the participants believed the computer would save what was typed; half believed the item would be erased. In addition, half of the participants in each of the saved and erased conditions were asked explicitly to try to remember the information. After the reading and typing task, participants wrote down as many of the statements as they could remember.

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