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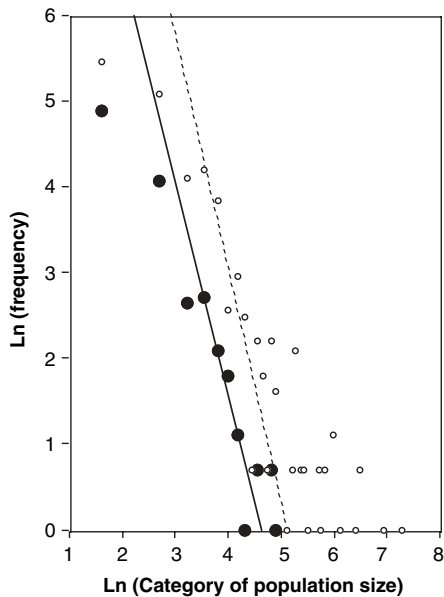
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**Fig. 4.** Log-log plot of population size versus frequency of population sizes for sites away from the influence of an *A. instabilis* colony (solid circles), and all data (small open circles repeat the data of Fig. 1). Slope is  $-2.48$ , fitted to the points located between 3.5 and 4.5 on the abscissa (17). The evident deviations from the power function at high population densities (small open circles) are not present in this data sample.

threshold (19)]. In a spatial context, if all bushes are occupied by scales and density dependence can be ignored, projecting the

overall population into the future is a simple matter of applying an exponential function to the total scale abundance. However, if that critical point where all bushes are occupied has not been reached, applying the simple exponential law will necessarily underestimate future population sizes, because the actual spatial dynamic will include newly occupied bushes in the future. Consequently, determining whether the system is at its critical value, at which point the application of the simple exponential would indeed be appropriate, has obvious practical importance. Thus, the degree to which spatial data adhere to a power function can be taken as an indication of the legitimacy of applying an exponential rule to population projections.

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15. S. Uno, unpublished data.
16. The site is located at Finca Irlanda, a 300-ha organic coffee farm in the Soconusco region of Chiapas, Mexico ( $15^{\circ} 11' N$ ,  $92^{\circ} 20' W$ ). The area receives about 4500 mm of rain annually and is located between elevations of 900 and 1150 m. According to a standard classification, the farm classifies as a commercial polyculture, with almost 100 tree species total.
17. Materials and methods are available as supporting material on Science Online.
18. Using 1000 coffee trees as the fixed habitat background, we drew a random number from a Poisson distribution (and truncated it to an integer) and generated the initial population density for each bush. The population density was then iterated as  $N(t + 1) = RN(t)$  for one time period, the first generation (where  $R$  is the finite rate of increase). We added to the result the number of individuals as determined from another random number generated from a Poisson distribution (and truncated to an integer), and this new number iterated for the second generation.
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20. We thank R. Friedland-Little, B. Chall, C. Taylor, G. Lopez, and G. Lin for help in gathering the data. M. Pascual read the manuscript and offered important advice. This work was supported by NSF grant DEB 0349388 to J.V. and I.P.

#### Supporting Online Material

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Materials and Methods  
Figs. S1 to S3

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## Nuclear Receptor Rev-erb $\alpha$ Is a Critical Lithium-Sensitive Component of the Circadian Clock

Lei Yin,<sup>1</sup> Jing Wang,<sup>1</sup> Peter S. Klein,<sup>2</sup> Mitchell A. Lazar<sup>1\*</sup>

Lithium is commonly used to treat bipolar disorder, which is associated with altered circadian rhythm. Lithium is a potent inhibitor of glycogen synthase kinase 3 (GSK3), which regulates circadian rhythm in several organisms. In experiments with cultured cells, we show here that GSK3 $\beta$  phosphorylates and stabilizes the orphan nuclear receptor Rev-erb $\alpha$ , a negative component of the circadian clock. Lithium treatment of cells leads to rapid proteasomal degradation of Rev-erb $\alpha$  and activation of clock gene *Bmal1*. A form of Rev-erb $\alpha$  that is insensitive to lithium interferes with the expression of circadian genes. Control of Rev-erb $\alpha$  protein stability is thus a critical component of the peripheral clock and a biological target of lithium therapy.

Genetic and biochemical analysis reveals that a 24-hour circadian rhythm is present throughout the animal kingdom (1–3). In mammals, circadian rhythm is a fundamental regulatory factor for many aspects of behavior and physiology, including sleep-wake cycles, blood pressure, body temperature, and metabolism (1–3). Disruption in circadian rhythms leads to increased incidence of many

diseases, such as cancer and mental illness (1, 3). Bipolar disorder in particular is associated with disturbed circadian rhythm (4).

Cells throughout the body also display 24-hour rhythms (3, 5). These are entrained by signals from a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is reset daily by light (3). Cellular rhythms are generated and maintained through

interconnected transcriptional feedback of clock genes (3, 6). The cycle starts when two bHLH-PAS domain proteins, BMAL1 and CLOCK, heterodimerize to activate a number of clock genes including *Per1*, *Per2*, *Cry1*, and *Cry2*. As a negative feedback loop, PER and CRY accumulate in the cytosol and then translocate into the nucleus, the PER-CRY complex inhibits its own transcription by binding to BMAL-CLOCK (3, 6–8). An additional negative feedback loop requires the transcription repression function of the orphan nuclear receptor Rev-erb $\alpha$ , which represses the transcription of *Bmal1* during circadian night and is responsible for rhythmic expression of the *Bmal1* gene (9–11). Rev-erb $\alpha$  itself is activated by BMAL1-CLOCK and thereby represents the link between the positive and negative loops of the circadian clock (9).

Posttranslational modifications also play an essential role in resetting the clock (2, 3, 12).

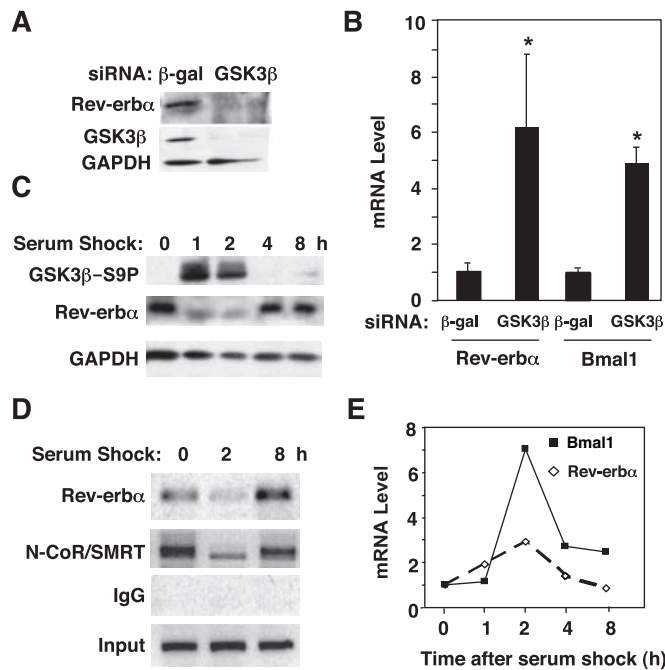
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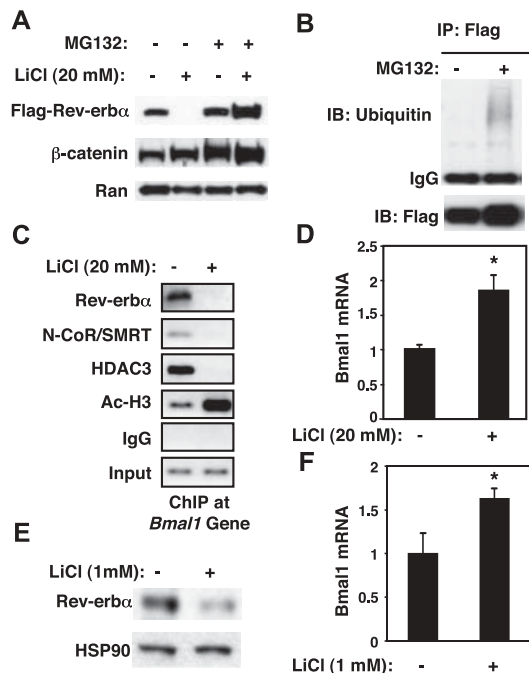
Phosphorylation of PER by casein kinase Iε leads to its ubiquitination and proteasomal degradation and, therefore, controls the period length in mammals as well as *Drosophila* (13). Mutation in *Shaggy*, the *Drosophila* homolog of glycogen synthase kinase 3β (GSK3β), lengthens the circadian period (12, 14), similar to the mammalian effects of lithium (15, 16), a potent and selective GSK3 inhibitor (17). We observed that the amino terminus of Rev-erba is serine-rich, with several potential GSK3β phosphorylation sites (fig. S1A). Remarkably, in human 293T embryonic kidney cells, reduced expression of GSK3β by small interfering RNA (siRNA) led to a near complete loss of endogenous Rev-erba protein (Fig. 1A), as well as ectopically expressed Flag epitope-tagged Rev-erba (fig. S2). This effect was posttranscriptional, as *Rev-erba* mRNA was increased dramatically by loss of GSK3β (Fig. 1B), consistent with the known function of Rev-erba protein to repress its own gene expression (18). *Bmal1*, the key circadian target of Rev-erba, was also markedly induced in cells lacking GSK3β (Fig. 1B). A similar reduction in Rev-erba protein was observed when a dominant-negative form of GSK3β was introduced into HepG2 cells by adenovirus-mediated delivery (fig. S3). These results suggest that GSK3β activity is required for stabilization of Rev-erba protein.

Next, we asked whether modulating GSK3β activity influences Rev-erba-mediated clock gene regulation. GSK3β is a constitutively active kinase that is inhibited by phosphorylation on serine 9 by multiple signaling pathways (19). We found that serum shock, which synchronizes circadian oscillations in cultured NIH3T3 mouse fibroblasts (5, 20), led to the immediate and robust phosphorylation of GSK3β at serine 9 (Fig. 1C). Remarkably, the level of Rev-erba protein plummeted during this time and recovered when the cells were returned to serum-free medium and GSK3β phosphorylation abated. The changes in the cellular Rev-erba protein were reflected by the cyclic occupancy of the *Bmal1* gene promoter by the nuclear repressor corepressor (N-CoR) that is recruited by Rev-erba (Fig. 1D), accompanied by transient induction of *Bmal1* and *Rev-erba* mRNAs (Fig. 1E).

GSK3β is also inhibited by lithium (17). Treatment of 293T cells with 20 mM LiCl dramatically down-regulated ectopically expressed Flag epitope-tagged Rev-erba without reducing the mRNA level (Fig. 2A; fig. S4). By contrast, endogenous β-catenin was stabilized by LiCl as expected (21). The destabilizing effect of lithium on Rev-erba was prevented by treatment of the cells with MG132, an inhibitor of the 26S proteasome (Fig. 2A). Inhibition of proteasome activity also prevented loss of Rev-erba due to siRNA inhibition of GSK3β (fig. S2A). Furthermore, we detected polyubiquitination of Flag-Rev-erba (Fig. 2B), indicating that



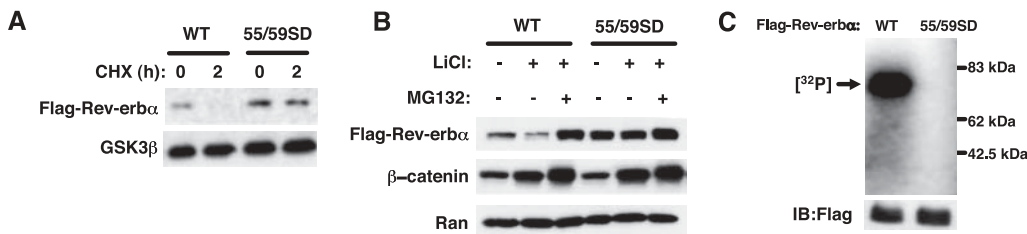
**Fig. 1.** GSK3β regulates Rev-erba protein amount and function. (A) Immunoblots of extracts from human 293T cells transfected with siRNA vector for either β-galactosidase (β-gal) control or human GSK3β. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as loading control. (B) 293T cells transfected with β-gal or GSK3β siRNA vector were analyzed for *Rev-erba* and *Bmal1* mRNA as described in methods (in the SOM). Shown is the mean ± SD of three experiments. \**P* < 0.05 versus control siRNA. (C) Immunoblots of extracts of mouse NIH3T3 cells subjected to serum shock (exposed to medium containing 50% horse serum at time 0 then switched to medium containing 0.5% bovine serum 2 hours later). (D) Chromatin immunoprecipitation (ChIP) for Rev-erba and the corepressors N-CoR/SMRT at the mouse *Bmal1* promoter in serum-shocked NIH3T3 cells. Rabbit IgG was used as nonspecific control. (E) Effect of serum shock on *Bmal1* and *Rev-erba* mRNA in NIH3T3 cells.



**Fig. 2.** Lithium reduces Rev-erba protein amount and function. (A) Immunoblots of extracts from 293T cells transfected with Flag epitope-tagged Rev-erba, and exposed to 20 mM LiCl and/or MG132. β-Catenin served as positive control for lithium effect on inhibition of GSK3β, and Ran guanosine triphosphatase (Ran GTPase) served as loading control. (B) Immunoprecipitation with Flag-specific antibody was performed from 293T cell extracts expressing Flag epitope-tagged Rev-erba treated with or without MG132. The ubiquitin-conjugated Rev-erba protein was detected by immunoblotting. (C) ChIP assay comparing the occupancy of endogenous Rev-erba, N-CoR/SMRT, HDAC3, and acetylated histone (Ac-H3) at the human *Bmal1* promoter of 293T cells treated with or without LiCl (20 mM, 16 hours). (D) Effect of LiCl (20 mM, 16 hours) on *Bmal1* gene expression in 293T cells. (E) Effect of LiCl (1 mM, 72 hours) on Rev-erba levels in 293T cells. Heat shock protein Hsp90 served as loading control. (F) Effect of LiCl (1 mM, 72 hours) on *Bmal1* gene expression in 293T cells. For RNA analyses, shown are the mean ± SD of three experiments. \**P* < 0.05 versus control treatment.

inhibition of GSK3β targets Rev-erba for degradation by the ubiquitin-dependent proteasome pathway. Lithium treatment also reduced the association of Rev-erba and the corepressor complex with the *Bmal1* promoter, while increasing histone acetylation (Fig. 2C) and gene expression (Fig. 2D).

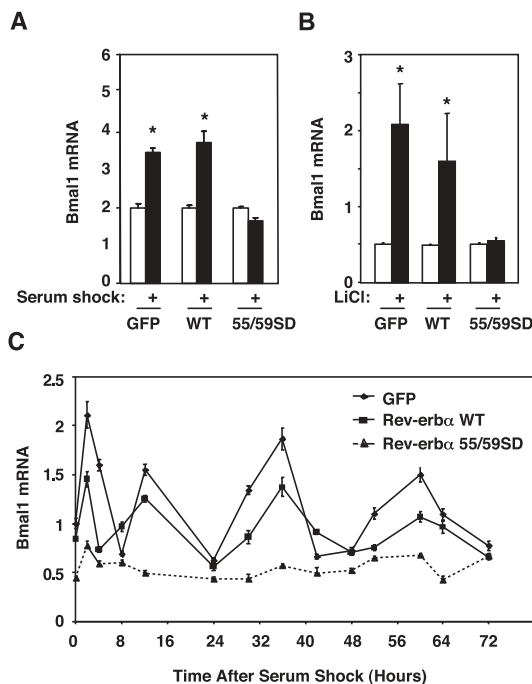
Although we have used lithium at a concentration of 20 mM to maximally inhibit GSK3β, chronic lithium therapy for patients with bipolar disorder aims for a serum concentration of ~1 mM (22). We therefore treated 293T cells with 1 mM LiCl for 72 hours and observed a marked reduction of Rev-erba protein (Fig. 2E) and



**Fig. 3.** Rev-erb $\alpha$  is stabilized by GSK3 $\beta$ -mediated phosphorylation of serines 55 and 59. (A) Immunoblots of 293T cells transfected with Flag-tagged Rev-erb $\alpha$  (WT or 55/59SD mutant), exposed to 25  $\mu$ g/ml cycloheximide (CHX) for 2 hours. (B) Immunoblots of 293T cells transfected with Flag-tagged Rev-erb $\alpha$  and treated with or without LiCl (20 mM) and MG132 (1 $\mu$ M). (C) In

vitro phosphorylation of Rev-erb $\alpha$  by GSK3 $\beta$ . HeLa cells were stably transfected with expression vector for WT or 55/59SD Flag-tagged Rev-erb $\alpha$ . Flag-tagged Rev-erb $\alpha$  protein was immunoprecipitated and incubated with [ $\gamma$ - $^{32}$ P]ATP (adenosine triphosphate) and recombinant GSK3 $\beta$  as in the SOM. Proteins were resolved on 12% SDS-polyacrylamide gel electrophoresis (SDS-PAGE) gel and analyzed by autoradiography (top) and immunoblot (bottom).

**Fig. 4.** Control of circadian gene expression by regulation of Rev-erb $\alpha$  protein stability. NIH3T3 cells stably expressing GFP, WT, or 55/59SD Rev-erb $\alpha$  were established. (A) Induction of mouse *Bmal1* gene expression in cells exposed to 50% horse serum for 2 hours. (B) *Bmal1* gene expression in cells exposed to 20 mM LiCl for 16 hours. (C) *Bmal1* gene expression in cells exposed to 50% horse serum for 2 hours, then switched to 0.5% horse serum for 72 hours. Shown are the mean  $\pm$  SD of three experiments. \* $P$  < 0.05 versus control treatment.



induction of *Bmal1* gene expression (Fig. 2F). Thus, degradation of Rev-erb $\alpha$  occurs at a clinically relevant concentration of lithium.

Within the Rev-erb $\alpha$  N terminus, serine 55 and serine 59 are located in a GSK3 $\beta$  consensus site that is identical in human, mouse, and rat (fig. S1B). Mutation of both amino acids to negatively charged aspartate (S55D/S59D, here shortened to 55/59SD) stabilized the protein (fig. S5). The 55/59SD mutant had a longer half-life and was resistant to lithium-induced degradation (Fig. 3, A and B). An in vitro kinase assay comparing the wild type (WT) and the 55/59SD mutant as substrate for GSK3 $\beta$  confirmed that these two serine residues were required for phosphorylation of Rev-erb $\alpha$  by GSK3 $\beta$  (Fig. 3C).

We hypothesized that early inactivation of GSK3 $\beta$ , causing Rev-erb $\alpha$  degradation and leading to *Bmal1* induction, is a critical step for synchronization of rhythmic expression of clock genes in NIH3T3 cells. To test this, we established stable NIH3T3 cell lines expressing green fluorescent protein (GFP, control), WT Rev-erb $\alpha$ , or 55/59SD Rev-erb $\alpha$ . *Bmal1* was induced by serum shock in GFP and WT cells,

but not in cells expressing the 55/59SD form of Rev-erb $\alpha$  (Fig. 4A). Moreover, *Bmal1* induction by lithium treatment was also absent in cells expressing the 55/59SD mutant (Fig. 4B). Lithium treatment also caused a significant change in the expression pattern of the clock gene *Per2* and the circadian output gene *Dbp* (23) in GFP and WT Rev-erb $\alpha$ -expressing cells, but not in cells expressing the Rev-erb $\alpha$  55/59SD mutant (fig. S6).

We performed further analysis to determine whether Rev-erb $\alpha$  degradation is required for the generation and maintenance of oscillatory gene expression over several circadian cycles. Remarkably, expression of the degradation-resistant 55/59SD form, but not WT Rev-erb $\alpha$ , severely dampened the oscillatory expression of *Bmal1* over three circadian cycles following serum shock (Fig. 4C). Thus, GSK3 $\beta$ -dependent regulation of Rev-erb $\alpha$  is important for synchronizing and maintaining the peripheral clock.

The GSK3 $\beta$  homolog *Shaggy* regulates the length of the circadian period in *Drosophila* (14), and mammalian GSK3 $\beta$  enzymatic activity oscillates with a 24-hour period both in SCN

and liver (16, 24). Moreover, a recent report identified a single nucleotide polymorphism within the GSK3 $\beta$  promoter that is associated with age at onset in bipolar depression (25). Circadian targets of GSK3 $\beta$  are beginning to be elucidated, with a recent study showing that GSK3 $\beta$  affects nuclear entry of mPER2 (16). Our results demonstrate that GSK3 $\beta$ -dependent stabilization of Rev-erb $\alpha$  maintains *Bmal1* in a repressed state and, more importantly, we have shown that the inability to degrade Rev-erb $\alpha$  is sufficient to prevent the onset of circadian gene oscillation. One or more components in serum that mimic external endocrine and/or neural cues induce phosphorylation and inactivation of GSK3 $\beta$ , resulting in the degradation of Rev-erb $\alpha$  and initiating the cycle of gene expression (fig. S7).

Lithium influences the circadian clock in humans, and circadian rhythms are altered in patients with bipolar disorder for which lithium is a common therapy (26). Here, we have shown that degradation of Rev-erb $\alpha$  is a critical target for lithium regulation of circadian gene expression. Intriguingly, histone deacetylase activity of the N-CoR/HDAC3 (histone deacetylase 3) corepressor is inhibited by valproic acid (27, 28), another mood stabilizer that modulates circadian rhythm (29), which suggests that this therapy may also target repression of clock genes by Rev-erb $\alpha$ . Given the toxicity of existing therapies, we suggest that novel approaches targeting Rev-erb $\alpha$  degradation may have potential in the treatment of bipolar and circadian disorders.

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30. We thank the University of Pennsylvania Diabetes and Endocrinology Research Center Vector Core (NIH DK 19525) and M. J. Birnbaum for GSK3 $\beta$  adenoviruses, and J. D. Alvarez and A. Sehgal for helpful discussions. Supported by NIH DK45586 (to M.A.L.) and NIH MH058324 (to P.S.K.).

### Supporting Online Material

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Figs. S1 to S7

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## On Making the Right Choice: The Deliberation-Without-Attention Effect

Ap Dijksterhuis,\* Maarten W. Bos, Loran F. Nordgren, Rick B. van Baaren

Contrary to conventional wisdom, it is not always advantageous to engage in thorough conscious deliberation before choosing. On the basis of recent insights into the characteristics of conscious and unconscious thought, we tested the hypothesis that simple choices (such as between different towels or different sets of oven mitts) indeed produce better results after conscious thought, but that choices in complex matters (such as between different houses or different cars) should be left to unconscious thought. Named the “deliberation-without-attention” hypothesis, it was confirmed in four studies on consumer choice, both in the laboratory as well as among actual shoppers, that purchases of complex products were viewed more favorably when decisions had been made in the absence of attentive deliberation.

Common knowledge holds that thorough conscious thought leads to good decisions and satisfactory choices. Whether purchasing a new car, a desktop computer, or a pair of shoes, people generally believe that serious conscious deliberation increases the probability that they will make the “right” choice. This idea applies especially to choices between products that are complex, multifaceted, and expensive. Whereas most people are willing to buy a new set of towels without much thought, they are unlikely to buy a new car or outfit a new kitchen without deliberation.

A second pervasive idea is that the quality of a choice benefits from “sleeping on it.” Rather than (or in addition to) thinking consciously, people usually feel that “unconscious thought” is useful for making sound decisions. Whereas conscious thought refers to thought or deliberation while conscious attention is directed at the problem at hand, unconscious thought can be defined as thought or deliberation in the absence of conscious attention directed at the problem (*1*). An example of unconscious thought is the following: One compares two holiday destinations (say the Costa Brava and Tuscany) and does not know what to decide. One puts the problem aside and

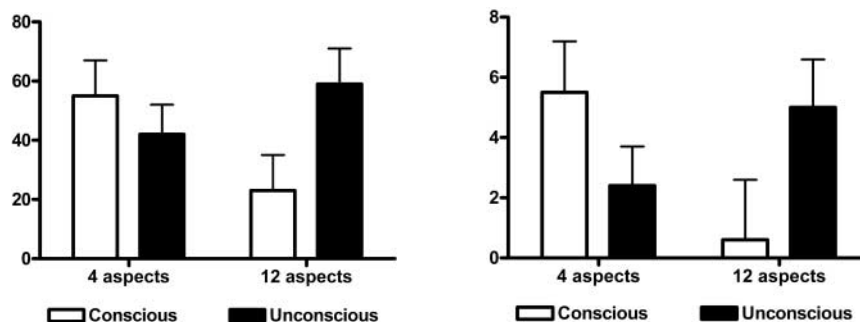
after 48 hours of not thinking about it consciously, suddenly the thought “It’s going to be Tuscany!” pops into consciousness. This thought itself is conscious, but the transition from indecision to a preference 2 days later is the result of unconscious thought, or of deliberation without attention.

The scientific literature has emphasized the benefits of conscious deliberation in decision making for hundreds of years (*2, 3*). The idea that conscious deliberation is the ideal (if not always attainable) way to approach a decision forms the backbone of classic (*4, 5*) as well as contemporary perspectives on decision making (*6, 7*) and attitude formation (*8, 9*). In contrast, the notion that unconscious thought is fruitful

hardly developed beyond the status of “folk wisdom.” It has been postulated or investigated by scientists infrequently [but see (*10–13*)]. The question addressed here is whether this view is justified. We hypothesize that it is not.

First, conscious thought does not always lead to sound choices. For example, participants who chose their favorite poster among a set of five after thorough contemplation showed less postchoice satisfaction than participants who only looked at them briefly (*14, 15*). Furthermore, conscious deliberation can make multiple evaluations of the same object less consistent over time (*16*). Two reasons why conscious deliberation sometimes leads to poor judgments have been identified. First, consciousness has a low capacity (*17, 18*), causing choosers to take into account only a subset of the relevant information when they decide (*13, 19*). Second, conscious thought can lead to suboptimal weighting of the importance of attributes (*13–16*): We tend to inflate the importance of some attributes at the expense of others, leading to worse choices.

Conversely, unconscious thought, or thought without attention, can lead to good choices (*13, 14*). In a recent experiment, participants read information about four apartments of different desirability (*20*). They were either asked to choose their favorite immediately, or given the opportunity to choose after a period of conscious thought, or distracted for some time



**Fig. 1.** Percentage of participants who chose the most desirable car as a function of complexity of decision and of mode of thought ( $n = 18$  to 22 in each condition). Error bars represent the standard error.

**Fig. 2.** Difference in attitude (on a scale of  $-25$  to  $+25$ ) toward the desirable and undesirable car as a function of complexity of decision and of mode of thought ( $n = 12$  to 14 in each condition). Error bars represent the standard error.

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