biochemical reconstitution of the entire VTC complex will be necessary to test this hypothesis.

Our identification of a eukaryotic polyP polymerase now allows investigating polyphosphate metabolism in fungi such as *Laccaria* (*21*) (fig. S9) that deliver polyP to the roots of their plant hosts, in diatoms such as *Thalassiosira* (*22*) (fig. S9), whose polyP pools form marine sediments (*5*), and in parasites where VTC is essential for osmoregulation (*23*). Because the VTC complex appears not to be conserved in animals or plants, another class of enzymes remains to be discovered that catalyzes phosphate polymerization in these organisms.

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16. Using recombinant Vtc4p* in vitro, we did not detect regeneration of ATP from ADP and either a polyP 3-, ~12-, or ~65-nucleotide oligomer.
17. Modeling of the nucleotide substrate in the opposite direction leads to severe clashes of the ribose and base portions with main chain atoms in the C-terminal helix in Vtc4p*. The position of this helical plug appears invariant in all crystal forms analyzed, making the helix unlikely to move upon substrate binding. Further, our assigned directionality of the nucleotide is consistent with the positions of the acceptor pocket and the polyP exit tunnel, respectively (Fig. 3, A and D, and fig. S3B).
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25. With the exception of the AppNHp-Mn^{2+} and PP_i complexes (determined at the Salk Institute), all crystallographic work was carried out at the European Molecular Biology Laboratory. We thank J. Noel, T. Gibson, and T. A. Steitz for discussion and J. Chory for generous support. This work was funded by the Peter and Traudl Engelhorn Foundation (Penzberg, Germany) and a European Molecular Biology Organization long-term fellowship (M.H), the Boehringer Ingelheim Fonds (A.U.), the German Science Foundation and the Landesstiftung Baden-Württemberg (K.S.), the Swiss National Science Foundation (A.M, P.O.H), and the National Science Foundation (IOS-0649389 to J. Chory). We thank the staff at the European Synchrotron Radiation Facility, Grenoble, France, at the Deutsches Elektronen Synchrotron, Hamburg, Germany, and at the Advanced Light Source, Berkeley, for technical support; and C. Müller and S. Cusack for sharing beam time. Coordinates and structure factors for $Vtc2p^{183\text{-}553}$ (PDB-ID 3g3o), Vtc4p*-polyP (3g3q), Vtc4p*-AppNHp-Mn^{2+} (3g3r), Vtc4p*-P_i (3g3t), and Vtc4p*- PP_i (3g3u) have been deposited with the Protein DataBank (www.rcsb.org).

Supporting Online Material

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Homeostatic Sleep Pressure and Responses to Sustained Attention in the Suprachiasmatic Area

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Throughout the day, cognitive performance is under the combined influence of circadian processes and homeostatic sleep pressure. Some people perform best in the morning, whereas others are more alert in the evening. These chronotypes provide a unique way to study the effects of sleep-wake regulation on the cerebral mechanisms supporting cognition. Using functional magnetic resonance imaging in extreme chronotypes, we found that maintaining attention in the evening was associated with higher activity in evening than morning chronotypes in a region of the locus coeruleus and in a suprachiasmatic area (SCA) including the circadian master clock. Activity in the SCA decreased with increasing homeostatic sleep pressure. This result shows the direct influence of the homeostatic and circadian interaction on the neural activity underpinning human behavior.

Maintaining optimal performance levels during evening hours may become difficult because increasing sleep propensity progressively overrides the wake-promoting circadian signal (*1*–*3*). Morning-type individuals wake up early and find it difficult to maintain performance in the evening (*4*). In contrast, evening types perform well in the evening hours (*4*) and seem to tolerate elevated sleep pressure in the evening better than morning types. Besides differences in circadian phase (*5*–*8*), morning types differ from evening types by a faster build-up of homeostatic sleep pressure during daytime (*9*) and by its faster dissipation during sleep (*10*, *11*). Taken together, these results support the notion that the circadian variation in waking performance also depends on homeostatic sleep pressure (*2*, *12*, *13*). Using functional magnetic resonance imaging (fMRI) in extreme chronotypes, we investigated the neural correlates of performance in the psychomotor vigilance task (PVT) (*14*–*16*), a simple reaction-time task that probes the ability to maintain sustained attention (*14*), which is modulated by circadian and sleep homeostatic regulatory processes (*17*).

Young, healthy participants of extreme morning (n = 16) or evening (n = 15) typology (*18*) were matched at the group level according to age, sex, and educational level and did not differ in their anxiety and depression levels or in sleep quality and daytime sleepiness (all P values > 0.1) (table S1). Participants were instructed to live according to their own preferred sleep-wake schedule for at least 1 week before the study (*16*). Afterwards, they reported to the sleep laboratory for two consecutive nights, where they were monitored by polysomnography at their preferred bedtimes (Fig. 1). The laboratory protocol started 7 hours before their habitual sleep time, which allowed for hourly assessments of subjective sleepiness (*19*) and objective vigilance (*14*), as well as hourly collections of saliva samples for assessment of circadian melatonin phase (*16*).

On average, bedtime, wake time, and circadian phase [estimated by the melatonin midrange crossing (MRC) time (*16*)] were about 4 hours earlier in morning than in evening types (all P values < 0.05) (table S1). These results indicate circadian phase entrainment with a similar phase angle (i.e., similar distance between MRC and bedtimes, P > 0.2) (table S1) in both chronotypes. One and a half hours (morning session) after scheduled awaken-

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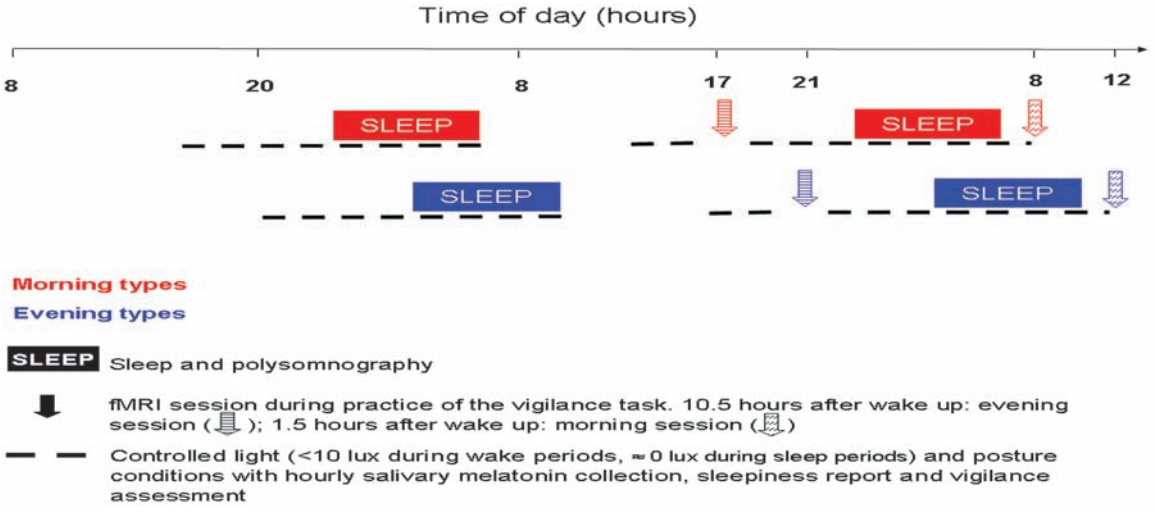

Fig. 1. Overview of the experimental design with sample time schedule for morning (red) and evening (blue) types. Subjects came to the laboratory 7 hours before scheduled sleeping time and stayed for two consecutive nights monitored via polysomnography. They stayed under controlled light (dashed line, <10 lux for wake periods, ≈ 0 lux for sleep periods) conditions and body posture. During the wake periods, sleepiness and vigilance measures were collected at hourly intervals and hourly saliva samples were assessed for melatonin. One and a half (morning session) and 10 and a half (evening session) hours after scheduled wake-up time and in a counterbalanced order, subjects underwent an fMRI session during the performance of the PVT task.

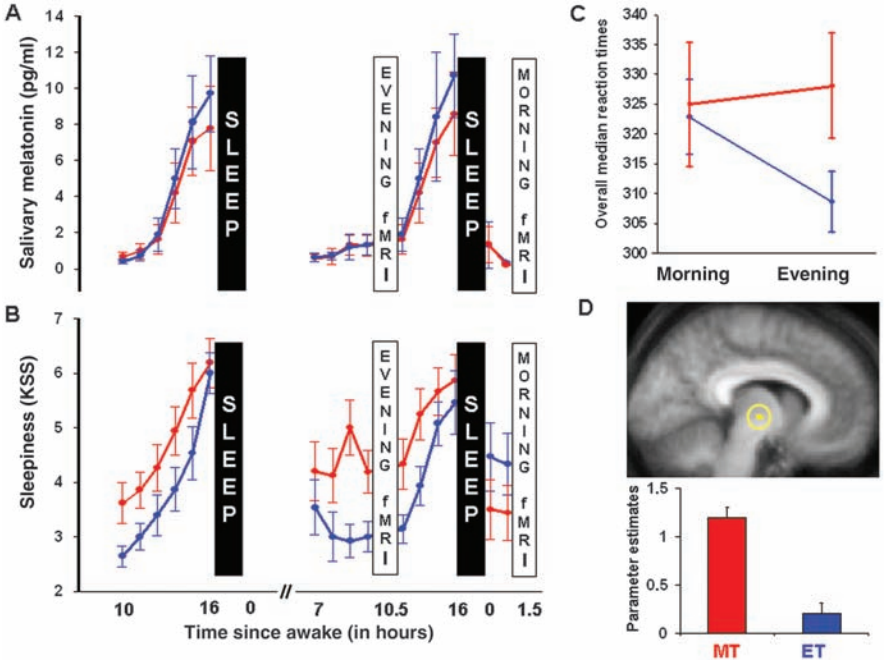

Fig. 2. (**A**) Time course of salivary melatonin in morning (red line) and evening (blue line) chronotypes. Hours spent since waking up throughout the protocol versus salivary melatonin as assessed by direct double-antibody radioimmunoassay. (**B**) Time course of daytime sleepiness (±SEMs) in morning (red line) and evening (blue line) chronotypes. Hours spent since waking up throughout the protocol versus self-reported values of sleepiness on the Karolinska Sleepiness Scale (KSS; higher scores correspond to increased sleepiness levels). (**C**) Overall median reaction times (±SEMs) according to time of day (morning versus evening) and chronotype (blue line: evening types, red line: morning types). (**D**) Increased thalamic response in morning as compared with evening types during the evening session. Display shows areas where blood oxygen level–dependent (BOLD) response is associated with the main effect of chronotype during the evening session for global alertness. Functional results are displayed at $P > 0.001$, uncorrected threshold, over the mean normalized structural magnetic resonance (MR) image of the population. Corresponding parameter estimates (arbitrary units) are plotted below the display [red, morning types (MT); blue, evening types (ET)].

ing, participants underwent a fMRI session during which they performed a PVT. The same protocol was administered 10.5 hours (evening session) after wake up on the other day (Fig. 1). This individually tailored design ensured equal amounts of time spent awake across chronotypes for the morning and the evening fMRI sessions, respectively.

The time course of salivary melatonin showed similar profiles according to the time spent awake in both morning and evening types (Fig. 2A) (interaction chronotype × melatonin profile: $P > 0.5$), which indicated comparable entrainment to the 24-hour cycle. Previously reported shorter circadian cycle length in morning than evening types (*20*) could potentially lead to a more advanced point of their circadian cycle after 10.5 hours of time spent awake, which would lead to a decreased circadian countersignal in morning types during the subjective evening hours. Although we cannot rule out such a possibility, our data do not indicate this, and we assume that both morning and evening types were tested at similar circadian phases during the morning and evening sessions.

The order of the morning and evening sessions was counterbalanced across subjects, and each scanning session was preceded by dim light conditions for at least 4 hours (<10 lux) (Fig. 1) to avoid the effects of bright light on circadian entrainment (*21*). During the evening fMRI session, evening types were less sleepy ($P < 0.05$) (Fig. 2B) (*16*) and tended to perform faster than morning types (overall median reaction times (RTs) ($P = 0.06$) (Fig. 2C) (*16*). No significant group differences in subjective sleepiness and sustained attention performance were observed for the morning session [all P values > 0.5 (*16*)]. These data indicate that under conditions of self-selected sleep-wake schedules, behavioral differences between chronotypes mostly prevail in the subjective evening hours, when the circadian wake-promoting signal has to counteract the homeostatic sleep pressure achieved after a normal waking day (*3*).

Our analyses of fMRI data tried to determine the neural correlates of successful sustained attention during the evening session, based on two behavioral measures that reflect different facets of attention. Trials associated with intermediate RTs (percentile 10 < RTs < percentile 90) corresponded to an average alertness level required to perform the task in a satisfactory manner, which is not compromised by the slowest RTs or by lapses associated with momentary task disengagement (*15*). We will refer to it as global alertness, deemed to be particularly sensitive to detect early effects of growing sleep pressure (*22*). In contrast, trials associated with fastest RTs reflect optimum response capabilities (*15*) that can be phasically recruited

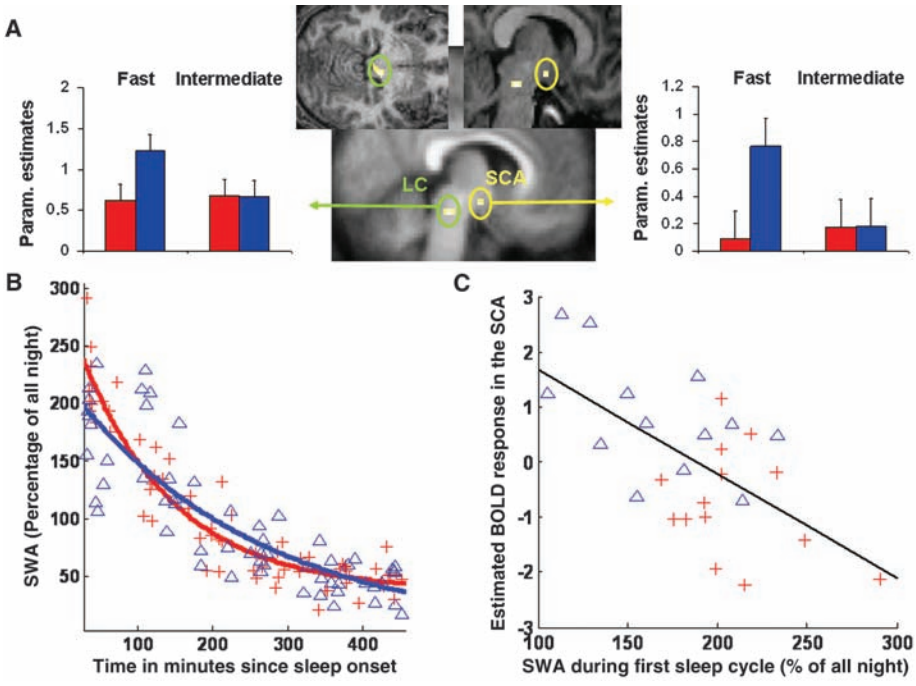

Fig. 3. (**A**) Increased task-related response in the dorsal pontine tegmentum and the anterior hypothalamus, compatible with the LC and SCA, respectively, in evening as compared with morning chronotypes during the subjective evening. Display shows areas where BOLD activity is associated with the main effect of chronotype during the evening session for optimal alertness. Functional results are displayed at $P > 0.001$, uncorrected threshold, over the mean normalized structural MR image of the population. Corresponding parameter estimates (arbitrary units) are displayed for event indicators of fast and intermediate reaction times (red, morning types; blue, evening types). (**B**) Exponential decay function [$SWA_t = SWA_\infty + SWA_0 \times e^{-rt}$ (*16*)] adjusted on relative SWA in sleep cycles (NREM sleep) measured from the central frontal derivation for all-night EEG of the night preceding the evening scan acquisition. Red crosses, morning types; blue triangles, evening types. SWA0 and *r* values are significantly higher in morning relative to evening types ($P > 0.05$). (**C**) Regression analysis of the relation between estimated BOLD responses during optimal task performance in the SCA region and the amount of SWA during the first sleep cycle in the preceding night ($r = 0.54$, $P < 0.05$, $n = 27$). Red crosses, morning types; blue triangles, evening types.

above and beyond the baseline cognitive level set by global alertness. To characterize this optimal vigilance component, fastest RTs (< percentile 10) were contrasted with intermediate RTs, which constituted an adequate global vigilance baseline.

Global alertness during the evening session was associated with larger responses in the thalamus in morning than in evening types (Fig. 2D, and table S4) (see table S3 for main effects of the task during the evening session). A similar enhancement of thalamic response by attention has been observed after sleep deprivation [e.g., (*23, 24*)]. No brain responses related to global alertness were significantly larger in evening than morning types during the subjective evening. In contrast, responses associated with optimal alertness were enhanced in evening relative to morning types, in a dorsal pontine tegmentum area and an anterior hypothalamic region. These areas encompass the locus coeruleus (LC) and the suprachiasmatic area (SCA), respectively (Fig. 3A, and table S4), two anatomically connected structures deeply involved in the circadian signal that promotes wakefulness and potentially regulates cognitive output during the waking state (*25*). These responses might result from differences in the ability to cope with increasing time spent awake during the subjective evening hours of a normal waking day, as already suggested by differences in subjective sleepiness levels (Fig. 2B). To test this hypothesis, we computed the slow wave activity (SWA; power spectral activity between 1 and 4 Hz) during non–rapid eye movement (NREM) sleep on the night preceding the evening scan session (*16*). The SWA observed during the first NREM sleep episode was considered to be a reliable estimate of the homeostatic sleep pressure (*26*, *27*) faced by the participant while performing the PVT during the fMRI evening session (see SOM (*16*)). In the frontal derivation, known to be most sensitive to variations in homeostatic sleep pressure (*28*), relative SWA was higher in morning than evening types at the beginning of the night (Fig. 3B) ($P < 0.05$) (*16*). SWA dissipation in the course of the night was also faster in morning than evening types (Fig. 3B) ($P < 0.05$) (*16*) resulting in similar SWA levels at the end of the night for both chronotypes ($P > 0.5$) (Fig. 3B) (*16*).

These findings confirm that morning and evening chronotypes differ in important parameters of sleep homeostasis. Furthermore, homeostatic sleep pressure turned out to be related to regional brain responses elicited by the PVT during the evening session, which might account for observed behavioral differences between groups. An independent regression analysis revealed that activity in the SCA was inversely proportional to the mean SWA recorded during the first NREM sleep episode (table S4 and Fig. 3C). This result suggests that activity in an area that includes the circadian master clock has a negative relation with indicators of sleep homeostatic pressure. It echoes similar findings obtained using long-term multiunit recordings of the suprachiasmatic nucleus (SCN) in rodents, which reported a decrease in SCN neuronal activity under conditions of increased sleep pressure (*29*). Conversely, lesions of the SCN in nonhuman primates resulted in an increase in total sleep time (*3*). These results indicate a direct interaction between sleep homeostasis and circadian rhythms in anterior hypothalamic areas. Consequently, we suggest that one of the key mechanisms accounting for behavioral differences between extreme chronotypes is that optimal alertness of morning-type individuals is jeopardized in the evening, because of a more pronounced negative influence of sleep homeostasis onto anterior hypothalamic structures involved in circadian regulation. Alternatively, it may be due to a lower circadian influence on sleep homeostasis arising from anterior hypothalamic areas. The ensuing decrease in local SCA activity is associated with decreased activity in brainstem structures promoting wakefulness, such as the LC, thereby diminishing their activating influence on the whole forebrain.

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Intuition and Deliberation: Two Systems for Strategizing in the Brain

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Dual-process theories distinguish between intuition (fast and emotional) and reasoning (slow and controlled) as a basis for human decision-making. We contrast dominance-solvable games, which can be solved by step-by-step deliberative reasoning, with pure coordination games, which must be solved intuitively. Using functional magnetic resonance imaging, we found that the middle frontal gyrus, the inferior parietal lobule, and the precuneus were more active in dominance-solvable games than in coordination games. The insula and anterior cingulate cortex showed the opposite pattern. Moreover, precuneus activity correlates positively with how "effortful" a dominance-solvable game is, whereas insula activity correlates positively with how "effortless" a coordination game is.

There are games in which, given sufficient computational capacity, each player can determine an optimal strategy using only the mathematical structure of the game. Checkers is a typical example; if each player plays optimally, then checkers must end in a draw (*1*). There are other games, though, in which players are required to coordinate their actions, and this requires a "meeting of the minds" that is not amenable to mathematical analysis. In this study, we contrast dominance-solvable games, where finding an optimal strategy is purely a mathematical problem, with pure coordination games, where successful play requires the players to go beyond the mathematics of the game (*2*).

A strategy is "dominated" if it is always worse than another strategy. Rational players eliminate all dominated strategies from consideration, creating a new game with fewer strategies, some of which may again be dominated. If this process can be iterated until a unique strategy remains for each player, then the game is dominance-solvable. Implementing this game-theoretic textbook procedure of step-by-step deliberation would likely require neural structures underlying cognitive processing, reasoning, and memory maintenance.

In a pure coordination game, each player's objective is simply to match the action of the other player (without communicating) (*3*). In "Nash equilibrium," both players choose the same action, but it is not possible to determine mathematically which action to choose, that is, on which Nash equilibrium to coordinate. In (*4*), participants were asked to name (among other things) a color, a number, and a year. When rewards did not depend on their answers, blue and red were about equally popular colors; the most popular numbers were 7, 2, and 10; and only 6.8% named the current year. However, when the game was turned into a pure coordination game, by rewarding those who matched the choices of others, red became by far the most frequent color, 1 the most frequent number, and 61.1% named the current year. Red, 1, and the current year had become "focal points," objects with "symbolic or connotative characteristics that transcend the mathematical structure of the game" (*5*). Automatic (fast, effortless) recognition of salient characteristics of complex high-dimensional objects is typical of intuitive judgments (*6*). Focal points must have properties that each participant recognizes as being salient not only to herself but also to others, but this too may be at least partly an intuitive judgment, using salience to oneself as an input. In general, intuition and deliberative reasoning are mental processes with very different properties. Intuition is fast, automatic, emotional, and effortless. Reasoning is slow, rule-governed, controlled, and effortful (*7*).

We designed two kinds of games, number games and box games. A dominance-solvable number game is shown at the top of Fig. 1A. Two players, X ("you") and Y ("other"), simultaneously pick a number from 0, 1, 2, or 3, without communicating. Each player's objective is to be as close as possible to a "target number." The instruction "other: you" means Y's target is "the number chosen by X," so Y wants to match X's choice. The instruction "you: other+1" means X's target is "one plus the number chosen by Y." A player who achieves her objective receives a reward [supporting online material (SOM), S1.2].

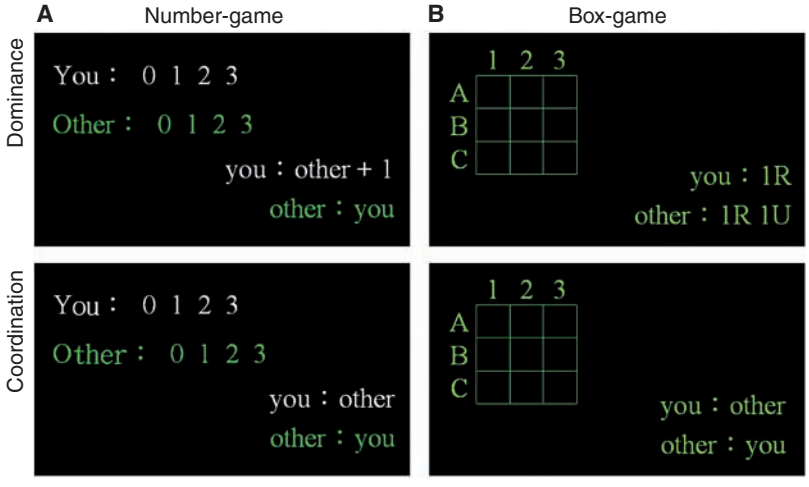

Fig. 1. Sample screens from the experiment. There are two conditions in the experiment: dominance-solvable games and pure coordination games. The condition in the top row is the dominance-solvable game and that in the bottom row is the pure coordination game. Targets of both players are shown in the lower right corner of each screen. In each game, each participant's objective is to be as close as possible to her target, which in turn depends on the choice of the other player (SOM, S1.2). There are two treatments. (**A**) In the number-game treatment, participants have to choose one number. (**B**) In the box-game treatment, participants have to choose one box.

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