International Journal of Comparative Psychology, 2001, **14**, 211-231.

Interval Timing and Genomics: What Makes Mutant Mice Tick?

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Mice can be shown to process temporal information as if they use an internal stopwatch that can be run, stopped, and reset on command and whose speed of "ticking" is adjustable. In addition, interval-timing behavior can be separated into clock, memory, and decision stages of information processing such that one stage can be modified without changing the others. In order to demonstrate the efficacy of interval-timing procedures in the evaluation of behavioral phenotypes, proline transporter (PROT) deficient mice (+/+, +/-, and -/-) were assessed for motor control (Rotarod beam), spatial memory (Morris water-maze), and temporal generalization (peak-interval procedure) competency. The findings demonstrate that interval-timing procedures can be profitably integrated into a behavioral battery and used to selectively diagnose the psychological abnormalities associated with transgenic, knock-out, and knock-down mouse models of human diseases.

Humans and other animals engage in a startlingly diverse array of behaviors that depend critically on the time of day or the ability to time short intervals. Timing intervals on the scale of many hours to around a day is mediated by the circadian timing system, while in the range of seconds to hours a different system, known as interval timing, is used (e.g., Hinton & Meck, 1997b). Recent research has illuminated some of the behavioral and neural mechanisms underlying the "internal clocks" of these two different timing systems in both animals and humans and has focussed attention on the brain mechanisms associated with interval timing (e.g., Hinton & Meck, 1997a). The term interval timing is used to describe the processes involved in the estimation and reproduction of relatively short intervals in the seconds to hours range. The classic example of interval timing comes from the fixed-interval (FI) procedure in which a subject's behavior is reinforced for the first response (e.g., lever press) made after a programmed interval has elapsed since the previous reinforcement. Subjects (e.g., primates, rodents, birds, and fish) trained on this procedure typically show what is known as the fixed-interval scallop. This pattern of behavior involves pausing after the delivery of reinforcement and starting to respond after a fixed proportion of the interval has elapsed despite the absence of any external time cues. Interval timing of this type has been identified in the majority of animals in which it has been tested for (e.g., Lejeune & Wearden, 1991; Paule et al., 1999; Richelle & Lejeune, 1980; Talton et al., 1999). The FI procedure gave rise to a discrete-trial variant known as the peak-interval (PI) procedure (Catania, 1970; Roberts, 1981) which is now widely used in studies of interval timing. In this procedure a stimulus such as a tone or light is turned on to signal the beginning of

This work was supported by grants AG09525 and MH544799 to WHM. The author would like to thank Aimee Benson and Lynn Talton for software development and animal testing. Correspondence concerning this article should be addressed to Warren H. Meck, Department of Psychological and Brain Sciences, Box 90086, Duke University, 9 Flowers Drive, Durham, NC 27708, U.S.A. (meck@psych.duke.edu).

the interval and in a proportion of trials the subject's first response after the criterion time is reinforced. In the remainder of the trials, known as probe trials, no reinforcement is given and the stimulus remains on for two or three times the criterion time. When the mean response rate in many probe trials is calculated an approximately Gaussian peak of responses is seen centered on the criterion. The time at which this timing function is at is maximum, also known as the peak time, gives an estimate of how accurately the subject is timing; precision is indicated by the spread of the timing function. It is these quantitative measures that make the PI procedure an attractive tool for the study of timing.

Behavioral data derived from tasks such as the PI procedure have contributed to the development of a number of different psychological theories of timing and time perception. A rich variety of behavioral, cognitive, and neuropsychological models of interval timing have been proposed (e.g., Church & Broadbent, 1991; Gibbon, 1977; Grossberg & Schmajuk, 1989; Ivry & Richardson, 2002; Killeen, 2002; Killeen & Fetterman, 1988; Lejeune, 1999; Machado, 1997; Miall, 1989; Staddon & Higa, 1999). These models can be organized into different categories based upon the types of timing mechanisms proposed (e.g., Church & Kirkpatrick, 2001; Matell & Meck, 2000). Of these theories, Scalar Expectancy Theory (SET) stands out because not only does it explain much behavioral data, but it has also been useful in interpreting and guiding pharmacological and anatomical work in the attempt to identify the brain mechanisms responsible for these behaviors (Gibbon et al., 1984; Gibbon et al., 1997). SET can be expressed as a computational theory of timing (e.g., Church, 2001) or as an information-processing model that postulates three distinct stages; a clock, a memory and a decision system as illustrated in Figure 1. The clock stage is hypothesized to consist of a pacemaker that emits pulses that are transferred to an integrator through a switch. When reinforcement occurs the current count in the integrator is transferred to reference memory. As training with a particular interval progresses a distribution of values in reference memory is formed. Finally if the animal needs to estimate or produce the learned interval this is done in the decision stage of the system by making a ratio comparison between the current value in the integrator and a random sample drawn from reference memory. Working memory can be engaged if trial-specific information is required to complete the timing of the stimulus, e.g., if the stimulus is interrupted by a gap or retention interval (e.g., Meck et al., 1984).

The Importance of Interval Timing in Cognitive Processing

It is becoming increasingly evident that interval timing is crucial for many forms of cognitive processing. One of the clearest cases comes from the field of optimal foraging which studies the extent to which animals' foraging decisions are the direct product of natural selection (for a review see Stephens & Krebs, 1986). In most cases to make decisions that maximize fitness an animal needs to measure its rate of food intake in one or more environments, and measuring rate requires measurement of time. Recent work has shown that European starlings are exquisitely sensitive to their rate of food intake, and appear to be recording the interval of time between each food they consume (e.g., Brunner et al., 1996; Kacelnik & Bateson, 1996; Kacelnik et al., 1990).

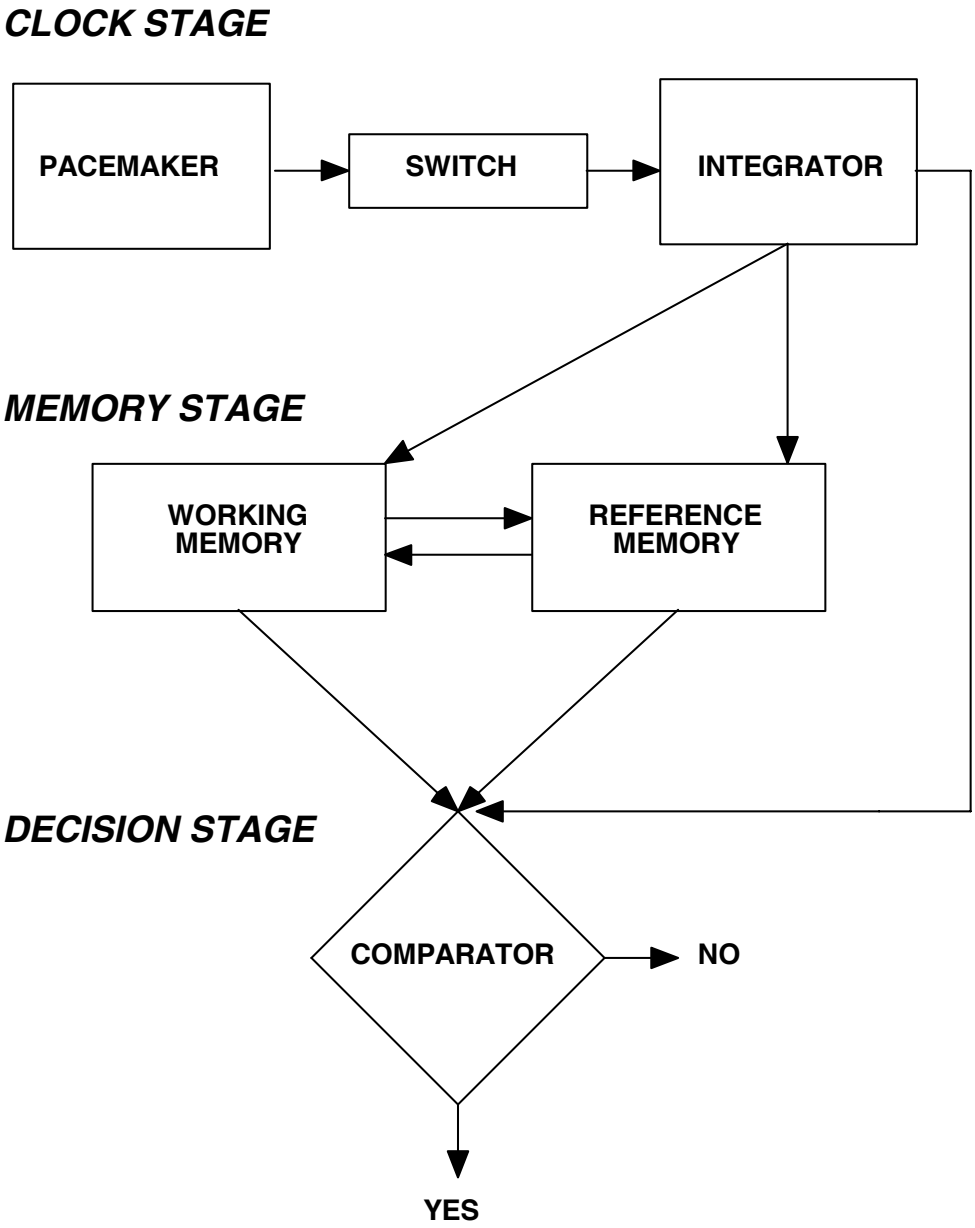

Figure 1. Information-processing model of interval timing.

Associative learning is emerging as another extremely widespread and important form of cognitive processing for which interval timing is important (Gallistel, 1990; Gallistel & Gibbon, 2000). In classical conditioning it is well established that the efficiency of learning about a conditioned stimulus (CS) is affected by the time interval between the CS and the unconditioned stimulus (US): in general terms it is found that the shorter the CS-US interval the faster and better the conditioning that occurs (e.g., Lucas et al., 1981). In fact it is not the absolute duration of the CS-US interval that is important as was initially thought, but the ratio of the CS-US interval to the interval between successive USs (Gibbon et al., 1977).

Human learning and memory is also highly sensitive to temporal processing and timing deficits have been observed in a variety of patient populations with damage to the basal ganglia, including Parkinson's disease and Huntington's disease patients (Malapani et al., 1998; Nichelli, 1993). Specialized techniques have been developed to study interval timing in humans using the brain imaging technologies of functional magnetic resonance imaging and event-related scalp potentials.

Connections Between Interval Timing, Neuropharmacology, and Drug Abuse

Drugs that increase the effective level of dopamine in the brain such as methamphetamine and cocaine are amongst the most commonly abused drugs today (e.g., Kuhn et al., 1998). The connection between timing and drug abuse comes from the fact that dopaminergic drugs cause predictable distortions in interval timing. The dopamine agonist methamphetamine causes a leftward shift in timing functions that is proportional in size to the duration of the interval being timed (Meck, 1983, 1996). This result is compatible with the hypothesis that increasing the level of dopamine in the brain causes an increase in the speed of the pacemaker used for timing: if the pacemaker is caused to run faster than when a time interval was first learned then animals will think that reward is due earlier than it actually is and consequently timing functions will be shifted to the left. It is reasonable to assume that abuse of methamphetamine in humans causes a similar speeding up of the clock to the increases observed in the lab with rats. Given the above evidence that interval timing is important both in the assessment of rate of reinforcement and in classical conditioning it has been hypothesized that timing distortions could be important in understanding the reinforcing properties of dopaminergic drugs.

Neural Basis of the Interval Clock

On the basis of the accumulation of evidence from drug and lesion studies some investigators have suggested a potential mapping between the information processing elements of SET and structures in the brain (e.g., Matell & Meck, 2000; Meck, 1996; Meck & Benson, 2002). Specifically, the output from dopaminergic neurons in the substantia nigra pars compacta has been suggested to serve as the "start gun" for interval timing. This hypothesis is supported by the observation that methamphetamine, that acts by facilitating the synaptic release of dopamine, speeds up the clock whereas haloperidol, which acts by blocking dopamine receptors, slows down the clock (e.g., Maricq & Church, 1983; Maricq et al., 1981; Meck, 1983, 1996). D2 dopamine receptors are specifically implicated in the function of the pacemaker by a study showing that the *in vitro* affinity of different neuroleptics for the D2 receptor predicts the size of the rightward shift in timing functions they produce (Meck, 1986).

As one can readily see, the ability of the brain to process time in the seconds to minutes range is a fascinating problem given that the basic electrophysiological properties of neurons operate on a msec time scale. One current model of interval timing integrates a multitude of cortical and thalamic oscillations with a "perceptron" processing system of the basal ganglia to arrive at the detection of times much larger than the oscillation periods (Matell & Meck, 2000). This model is based on the observation that striatal spiny neurons receive 10,000-30,000 separate inputs

from a wide variety of cortical and thalamic areas. These cortical and thalamic neurons oscillate with a mean periodicity of 10 Hz (Llinas, 1993, 1998). The striatal spiny neurons have been hypothesized to be capable of detecting and responding to select patterns of cortical input. The particular pattern of excitatory input is selected by long-term potentiation and/or long-term depression which is believed to result from dopaminergic activity from the midbrain (e.g., substantia nigra pars compacta and the ventral tegmental area) following the delivery of reinforcement. Additionally, these dopamine neurons have been shown to transfer their activation onset to the signals that predict subsequent reinforcement (Schultz et al., 1993, 1997).

The above neurobiological properties of the cortico-striatal circuitry can be combined with a "beat frequency" model of timing (Miall, 1989) that suggests that after resetting a range of oscillatory inputs, a specific time can be encoded by selectively weighing which inputs are currently active at the criterion time. This model's time coding is similar to the idea that one can code the number 15 by asking for the lowest common multiple of 3 and 5, thereby coding large numbers with much smaller numbers. Thus, the model provides a manner to encode a long interval with very short neuronal mechanisms using the concept of coincidence detection which has been hypothesized as a function of basal ganglia information processing (e.g., Houk, 1995).

Specifically, upon onset of a meaningful signal (e.g., a cue that predicts important outcomes), dopamine neurons fire in a burst pattern which transiently synchronizes the cortical and thalamic oscillations, as well as hyperpolarizes the striatal membrane, thereby resetting the integrating mechanism. The cortical and thalamic neurons begin to oscillate at their inherent periods, thus eliminating their synchronization and allowing particular patterns of activity to become meaningful. Upon detection of a previously reinforced pattern of input, via the crossing of a coherent activity threshold (set by baseline levels of dopamine input and striatal interneurons), an ensemble of striatal spiny neurons fire, thereby engendering a response that the encoded time has been reached. This striatal activity passes out of the basal ganglia to the thalamus and from there back to the cortex and striatum, thereby impinging on the current oscillatory inputs, allowing alterations of timing and time perception (Matell & Meck, 2000). Such information flow through cortico-striato-thalamo-cortical loops has been observed in functional magnetic resonance imaging (fMRI) data during psychophysical timing tasks with human subjects (e.g., Hinton et al., 1996; Meck et al., 1998).

What Makes a Mutant Mouse "Tick"?

The study of timing and time perception in wild-type and mutant mice has been successfully demonstrated and promises to become a fruitful area of inquiry for the study of the molecular basis of learning and memory (e.g., Abner et al., 2001; Carvalho et al., 2001; Cevik, 2001; Huerta et al., 2000; Sasaki et al., 2001). For example, mice that display impairments in synaptic plasticity both at the presynaptic (synapsin I, synapsin II, synaptotagmin I, synaptogyrin and synaptophysin) and postsynaptic (alfaCaMKII Thr286Ala) level have been evaluated for their ability to form stable representations of event durations using the PI timing procedure (e.g., Carvalho et al., 2001). These data suggest that impairments in the acquisition

and retention of temporal memory are related to presynatic alterations in neural plasticity.

The major questions that many of these researchers seem to be asking about the internal clock used to make temporal discriminations in the seconds to minutes range are: What makes a mutant mouse "tick"? Or to put it another way, what brain mechanisms are involved in interval timing and what types of changes in interval timing are possible and/or interpretable using mutant mice? What follows is an outline of some of these possibilities.

(1) The accuracy of a temporal discrimination can be affected by selective alterations in memory storage and retrieval processes. This type of change in interval timing has been described as a modification of the memory translation constant (K*) which is a multiplicative (i.e., scalar) constant (Meck, 1983, 1996; Gibbon et al., 1984). Animals typically represent the psychological time of reinforcement veridically with the physical time of reinforcement, thus displaying a K* of 1.0. Systematic discrepancies in the psychological time of reinforcement can occur, however, with K* < 1.0 and K* > 1.0 leading to durations being remembered as being proportionally shorter or longer, respectively (Church & Meck, 1988; Meck, 2002a, 2002b; Meck & Church, 1987). Searching for a K* mutant is logically similar to the identification of the hamsters, mice, and fruit flies bearing the circadian tau mutation. One caveat to keep in mind is that it seems unlikely to some researchers that this could be a single gene in the case of interval timing because of the reliance on the interactions of distributed brain areas, including frontal-striatal circuitry, rather than on rhythmic activity sustained by individual cells within the suprachiasmatic nucleus (e.g., Allada et al., 2001; Hinton & Meck, 1997; Lowrey et al., 2000; Ralph & Menaker, 1989).

(2) The precision of a temporal discrimination can be modified by selective alterations in the sources of variability associated with interval timing (e.g., Church et al., 1994). Precision and/or sensitivity to time can be affected by the speed and variability of the internal clock as well as by variability in memory and the thresholds used to control responding. In practice, alterations in clock speed would be the primary factor of interest. Animals with higher clock speeds should (everything else being equal) exhibit greater sensitivity to duration and enhanced precision (e.g., Brunner et al., 2001). In contrast, animals with lower clock speeds should exhibit a lower sensitivity to signal durations and impaired precision in timing behavior. The identification of these sources of variability can be a pain-staking process, but it is feasible with current behavioral procedures and data analysis techniques (e.g., Cheng et al., 1993; Gibbon & Church, 1984; Church et al., 1994; Rakitin et al., 1998).

Genes that modify clock speed should be identifiable with the combined use of pharmacological agents known to increase (e.g., methamphatamine) or decrease (e.g., haloperidol) clock speed in wild-type animals. Changes in clock speed lead to the observed clock pattern induced by dopaminergic manipulations (e.g., Meck, 1983, 1996). It would, of course, be possible to selectively knock out the clock – an extreme form of slowing it down. Presumably tyrosine hydroxylase knock-out (–/–) mice would have a completely dysfunctional internal clock, but this is hardly a selective manipulation unless it is limited to the substantia nigra pars compacta or the ventral tegmental area (e.g., Suri et al., 1993). Dopamine transporter (DAT) knock-out and knock-down mice are also of great interest in this regard and have been

shown to demonstrate paradoxical effects to dopaminergic drugs (e.g., Cevik, 2001; Jones et al., 1999; Gainetdinov et al., 1999; Giros et al., 1996).

Other types of changes in the functioning of the "internal clock" are also possible. These might include: **(3)** The rate of acquisition of a temporal discrimination, e.g., the setting of response thresholds (upper and lower thresholds in the PI procedure) can be selectively modified (e.g., Church et al., 1994; Meck & Church, 1984). Differences in the thresholds to start and stop responding would be expected to affect the symmetry of the response distributions and the degree of independence in the setting of these proportional thresholds (e.g., Church et al., 1994; Church et al., 1991).

(4) Changes in the probability of attention and/or attentional time-sharing (e.g., the latency to start and stop timing, or the ability to divide attention among multiple events or signal durations as in simultaneous temporal processing (e.g., Fortin & Massé, 2000; Meck, 1984, 1987; Pang et al., 2001; Penney et al., 1996; Meck & Williams, 1997).

(5) Changes in working memory or the ability to bridge a retention interval or break inserted into the ongoing timing signal (e.g., "gap" procedure) have demonstrated the involvement of the hippocampus in interval timing (e.g., Buhusi & Meck, 2000; Fortin & Massé, 2000; Meck, 1988; Meck et al., 1984; Meck et al., 1987).

(6) Selective changes in the range of intervals that can be timed (e.g., the possibility of missing oscillators). Assuming that a continuum of oscillators are used to time a wide range of signal durations, it would be possible that a mutation could lead to the effective deletion of one or more of these oscillators. Such a deletion could result in the inability to time specific durations (i.e., a loss in sensitivity to certain ranges of durations). This would tend to increase the discontinuities or nonlinearities that are sometimes observed in interval timing behavior (e.g., Crystal, 1999, 2001; Crystal et al., 1997).

(7) Individual trials taken from PI timing sessions can be analyzed for sequential dependencies and also for their covariance patterns. Unlike the mean response rate functions, individual peak trials are not typically characterized by a gradual increase and then a decrease in response rate centered around the time of reinforcement, but by a period of a relatively constant, high response rate, preceded and followed by a low response rate. The covariance pattern among measures of the temporal characteristics of the high response rate (start, stop, middle, and spread) have been shown to support a parallel, scalar timing model in which animals used on each trial a single sample from memory of the time of reinforcement and separate response thresholds to decide when to start and stop responding. Analysis of individual trials can also assist in the identification of the sources of variance (e.g., clock, memory, and decision) in temporal discriminations (e.g., Church et al., 1994).

In order to illustrate how interval-timing procedures can be used to evaluate mutant mice it might be useful to provide a specific example. The expression of a brain-specific, high-affinity Na+/Cl--dependent l-proline transporter (PROT) in subpopulations of glutamatergic pathways in the mammalian brain suggests a physiological role for this carrier in excitatory neurotransmission (e.g., Fremeau et al., 1992; Renick et al., 1999). It has been found that proline can potentiate synaptic transmission and various investigators are utilizing mouse mutants to investigate the mechanisms by which it does so (e.g., Cohen & Nadler, 1997). Consequently, in

order to investigate the role of the PROT in behavior we studied PROT knock-out (+/– and –/–) and wild-type (+/+) mice in tests of motor control (Rotarod test), spatial memory (Morris water maze), as well as timing and temporal memory (PI procedure).

Method

Subjects

Thirty-one male proline knock-out mice (wild-type = 11; heterozygous = 9; homozygous = 11) were housed in groups of 4-5 per cage and segregated by genotype. The mice were approximately 4 months of age at the beginning of the experiments and were maintained at 85% of their free-feeding weight with free access to water in the home cage. The colony room was on a 12:12 light:dark cycle at 21° C and 40-70% humidity.

Rotarod Procedure

Each mouse was placed on a rod rotating at 24 rpm (Economex Rota-Rod, Columbus Instruments, Ohio, U.S.A.) and the time to fall off was measured up to a 5 min maximum. A single trial was given each day for 10 consecutive days.

Morris Water-Maze Procedure

Baseline Training. Mice were individually placed in a 1.1 m diameter/30.5 cm deep pool of water maintained at 22–24° C and allowed up to 120 s to locate a 10.5 cm platform hidden under the surface of the water. The water was colored with white tempora paint in order to conceal the location of the platform. The swim path and latency to locate the platform was recorded using a digital tracking system (HVS Image, Hampton, United Kingdom). Four different platform locations were used and these were counterbalanced across treatment groups. Once the platform was located the mice were allowed to wait there for 60 s before being removed from the pool. If the mice did not locate the platform within 120 s they were manually placed on the platform. Mice were given 18 consecutive days of baseline training.

Probe Trial Testing. Five days after the last day of baseline training the mice were tested for their memory of the platform location used during the previous 18 consecutive days of baseline training. During the probe trial the platform was removed from the pool and the number of times that the mouse passed through the former platform location during the 60-s trial was recorded. A larger number of passes would be expected to reflect better spatial memory (i.e., greater resistance to forgetting and/or interference).

Peak-Interval Procedure

Four mice from each of the genotypes were randomly selected for testing in twelve identical Med Associates (Vermont, U.S.A.) stainless steel and plexiglass chambers designed for mice. Chambers contained three ultra-sensitive response levers aligned in a row across the front of the chamber, stimulus lights were located above the levers, a pellet dispenser for the delivery of 20 mg precision food pellets, formula A/I (P. J. Noyes, New Hampshire, U.S.A.) into a food cup beneath the center lever, and a speaker on the back wall of the chamber. Each chamber was contained in a light-and sound-attenuating cubicle and was equipped with a house light and fan for ventilation.

Autoshaping

Mice were trained to lever press in six daily one hour sessions. During these sessions, a food pellet was delivered once a minute for sixty minutes. In addition, one of the side response levers (e.g., left lever) was primed until fifteen reinforced responses were made on that lever at which point, the middle response lever was primed for the reinforcement of fifteen responses and finally

the other side lever (e.g., right lever) was primed for the reinforcement of fifteen responses. In addition to the operant contingency, a Pavlovian contingency was also in effect. During the time that the side levers were primed for response-dependent reinforcement, the primed lever was retracted for a duration of 1 s, 2 s before the response-independent delivery of a food pellet. This produced a conditioned stimulus (CS = moving lever) paired with an unconditioned stimulus (US = food). The direction in which the levers were primed (e.g., left lever, middle lever, right lever) was counterbalanced across mice. This procedure was repeated until the mouse pressed each lever 30 times or 60 minutes had passed, thus ending the session.

Fixed-Interval Training

Phase I sessions began with the illumination of the houselight and the onset of a 93 dB tone. A 10-s fixed-interval (FI) schedule of reinforcement was programmed for either the right or the left response lever (counterbalanced across mice). The first response after 10 s was reinforced with a 20-mg food pellet and the auditory stimulus was turned off. After a 2-s delay, the auditory stimulus was turned back on and a 30-s FI schedule was imposed for responding on the middle lever. Following reinforcement of the appropriate lever press, the auditory stimulus was again turned off for 2 s. The auditory stimulus was then turned on again and a 90-s FI schedule was programmed for responding on the remaining side lever. After reinforcement was earned for this lever, the auditory stimulus was turned off and a random intertrial interval (ITI = 55 s mean, range 40-70 s) was initiated. This procedure was repeated for 95 min. The within-trial 2-s breaks inserted among the increasing FI values were used to "transition" the mouse from one side of the operant chamber to the other during the sequential 10-s, 30-s, 90-s trial components. For each FI, the trial would self terminate if the mouse did not make a response after the criterion duration and before three times the criterion duration plus a random 0-20% of the 3x criterion duration (e.g., a 30-s FI trial during which no responding occurred could last anywhere from 90 to108 s). This phase of training lasted for approximately 20 sessions.

Phase II sessions were identical to those described above with the exception that, on any particular trial, the temporal criterion for priming reinforcement was randomly selected from the three FI values (10, 30, and 90 s) with replacement, and the full 55 s ITI was instituted after every trial. In these trials, the mouse did not have any cues as to which temporal criterion was in effect. Consequently, the mice learned to initiate each trial by pressing on the “short” lever. If this lever did not pay-off, the mouse would then switch to the “intermediate” lever. If again this lever failed to pay-off, the mouse would switch to the “long” lever, for which reinforcement would be guaranteed to occur for the first response after 90 s. Under this design, the 10-s, 30-s, and 90-s FI’s were each randomly primed on approximately 33% of the trials. This phase of training lasted for approximately 20 sessions.

PI Testing. These sessions were identical to the FI training described above with the exception that a nonreinforced probe trial was added to the trial types randomly selected for each trial. These nonreinforced probe trials lasted for the same length of time as the selfterminating 90-s FI trials (e.g., 270-330 s). This design allowed for 25% of the trials that lasted at least 10 s to be primed for reinforcement, 33% of the trials that lasted at least 30 s were primed for reinforcement, and 100% of the trials that lasted at least 90 s were primed for reinforcement (i.e., no nonreinforced probe trials were included for the 90-s FI trials due to concerns about a loss of responding on these extinction trials; see Matell & Meck, 1999, for additional procedural details). This phase of training lasted for approximately 20 sessions.

PI Testing with Gaps. Two test sessions were given in which a 5-s gap was inserted into the auditory signal 15-s after signal onset on a random 50% of the 30-s probe trials. This peak-interval procedure with gaps served as a test of whether or not mice could retain the duration of the signal prior to a gap and add it to signal duration following a gap in order to determine their response. No reinforcement was provided on gap trials (see Meck et al., 1984, for additional details on the application of the gap procedure).

Data Analysis

Only data from nonfood probe trials were analyzed. In addition to the analysis of mean response rate functions, individual trials were also examined. For the analysis of individual trials the

time that the mouse began responding and stopped responding on each lever was determined by fitting a "low-high-low" step function to the data as described by Church et al., (1994). This allowed for the calculation of the start time (s_1) for responding, the stop time (s_2), the spread (d) of the high response state defined (by $s_2+s_1/2$), the center (c) of the high state, and the mean response rate (r) of the high state for the 10-s and 30-s criteria. Because, by definition, s_2 must be greater than s_1, there would be a positive relationship between these variables if points were placed at random within this constrained space. To reduce this bias for a positive relationship between the time of starting and stopping in random data, we analyzed data only from nonfood trials in which s_1 was less than or equal to the time of reinforcement and s_2 was greater than the time of reinforcement on each lever (i.e., good starts and stops). Previous studies with rats and pigeons have shown a consistent pattern of positive correlations between the start and stop so that the animals tended to stop later on trials on which they started later than usual (e.g., Cheng & Westwood, 1993; Church et al., 1994). A consistent pattern of negative correlations between the start and the spread has also been observed, such that animals tended to respond longer in the high state when they started earlier than usual. In addition, a consistent pattern was observed in the positive correlation between the spread and middle, so that animals tended to center their high state later when they responded longer in the high state than usual (e.g., Church et al., 1994).

Results and Discussion

Rotarod Test of Motor Function

As illustrated in Figure 2, no group differences were observed in motor ability as measured by the Rotarod test across the 10 sessions: Treatment, $F < 1$ (alpha set to 0.05 in all statistical tests); Trial Block, $F(9, 252) = 1.68$; and Treatment x Trial Block interaction, $F(18, 252) = 1.19$. These results indicate that there are no discernible weakness in the motoric abilities of PROT knock-out mice and that all treatment groups acquire this motor task at approximately the same rate.

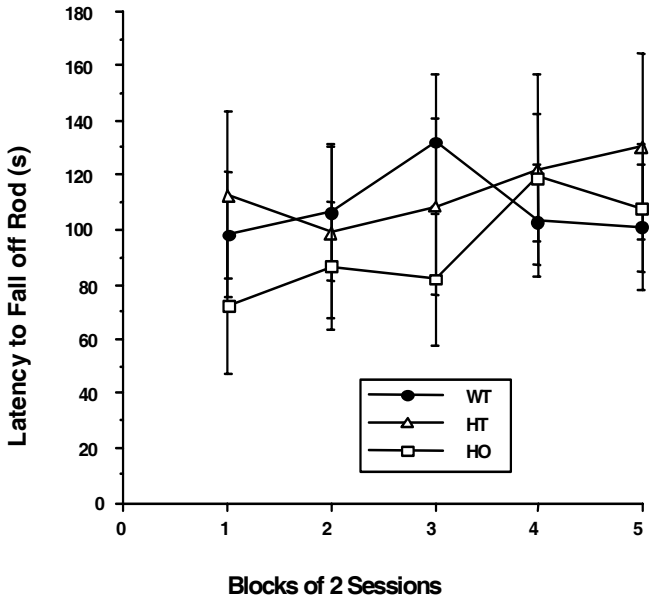

Figure 2. Mean ± standard error of the latency to fall off the Rotarod beam moving at 24 rpm with a 5 min maximum. Data are plotted as a function of 2-session blocks for Wild-Type (WT), Heterozygous (HT), and Homozygous (HO) PROT-deficient mice.

Morris Water-Maze Tests of Spatial Memory

There were no significant differences in performance as a function of platform location and the data were collapsed across this variable. As illustrated in Figure 3, no significant treatment differences were observed in the acquisition phase (Sessions 1-18) of the Morris water-maze in terms of the latency to locate the platform: Treatment effect, $F < 1$; a significant effect of Trial Blocks, $F(5, 140) = 22.9$; and Treatment x Trial Blocks interaction, $F(10, 140) = 1.71$. These results again indicate no differences in swimming speed or the ability to learn the location of the hidden platform.

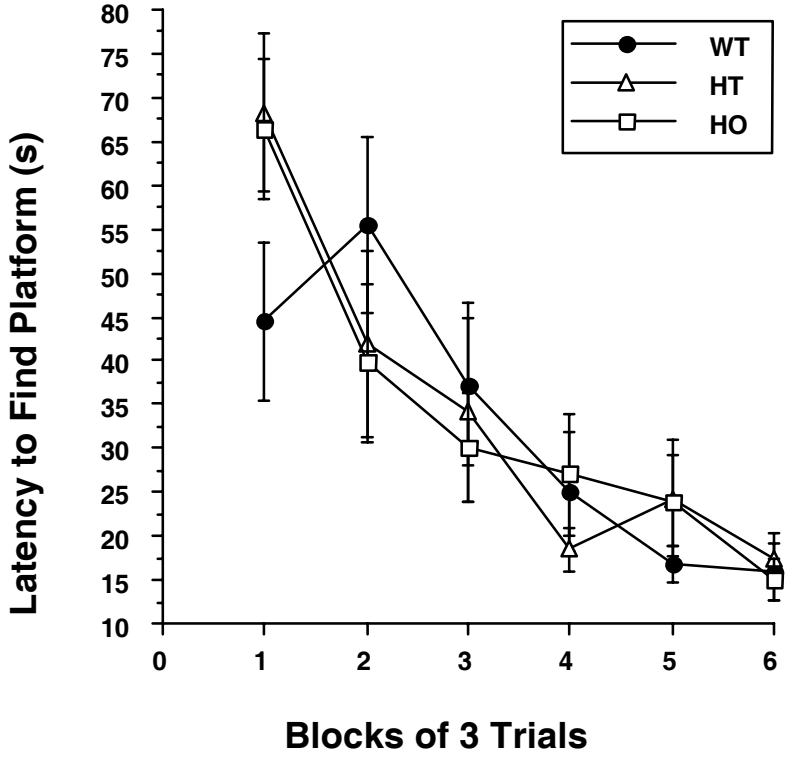

Figure 3. Mean ± standard error of the latency to locate the hidden platform in a Morris water-maze with a maximum latency of 120 s. Data are plotted as a function of 3-trial blocks for Wild-Type (WT), Heterozygous (HT), and Homozygous (HO) PROT-deficient mice.

In contrast, as illustrated in Figure 4, when the memory for the location of the platform was tested following a 5 day retention interval the mice showed significant treatment differences in the number of passes they made through the platform location. *Probe trial memory test*: Treatment effect, $F(2, 28) = 4.48$; Trial Block (s), $F(3, 84) = 142.96$; and Treatment x Trial Block (s) interaction, $F(6, 84) = 2.32$. The 60-s probe trial data indicate that PROT-deficient mice (both +/- and -/-) have impairments in their ability to maintain information in spatial memory when tested

for 60-s at a 5-day retention interval. It would be important to study this effect parametrically by varying the length of the retention interval in order to determine whether any +/- versus -/- differences might be observed and at what point in time these mice begin to diverge from the wild-type mice in terms of their spatial memory function.

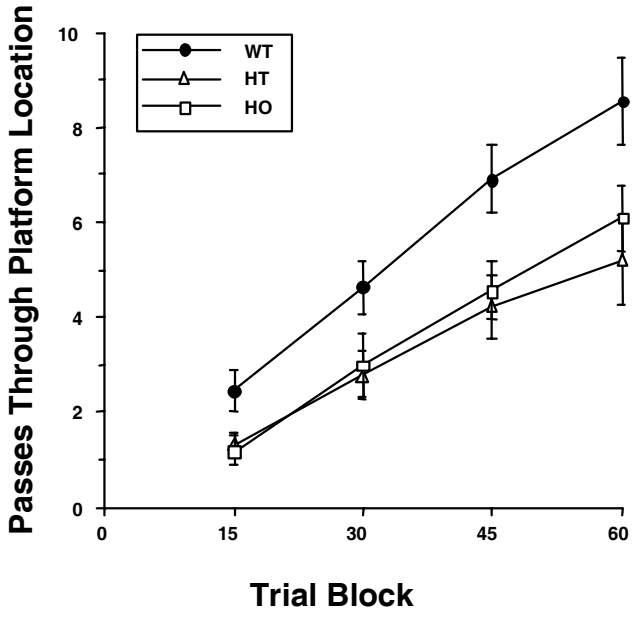

Figure 4. Mean ± standard error of the cumulative number of passes through the platform location on the single probe session which occurred 5 days after baseline training. Data are plotted as a function of 15-s blocks within the 60-s trial for Wild-Type (WT), Heterozygous (HT), and Homozygous (HO) PROT-deficient mice.

PI Tests of Timing and Temporal Memory

Mean response rate as a function of signal duration, lever, and treatment group are shown in Figure 5. Measures for peak time (s), peak rate (responses/min), and spread (s) for these function are presented in Table 1. No significant treatment differences were observed in the remembered times of reinforcement as measured by peak time, although as expected, there was a significant effect of the FI value on the obtained peak times: Treatment, $F(2, 6) = 1.45$; Duration, $F(1, 3) = 337.15$; and Treatment x Duration interaction, $F < 1$. Similarly, there were no significant differences in the levels of responding as measured by peak rate: Treatment, $F < 1$; Duration, $F < 1$; and Treatment x Duration interaction, $F < 1$.

In contrast, there were significant treatment differences observed in the spread of the peak functions as shown in Figure 6: Treatment, $F(2, 6) = 104.53$; Duration, $F(1, 3) = 375.0$; but a nonsignificant Treatment x Duration interaction, $F(2, 6)$ 3.95.

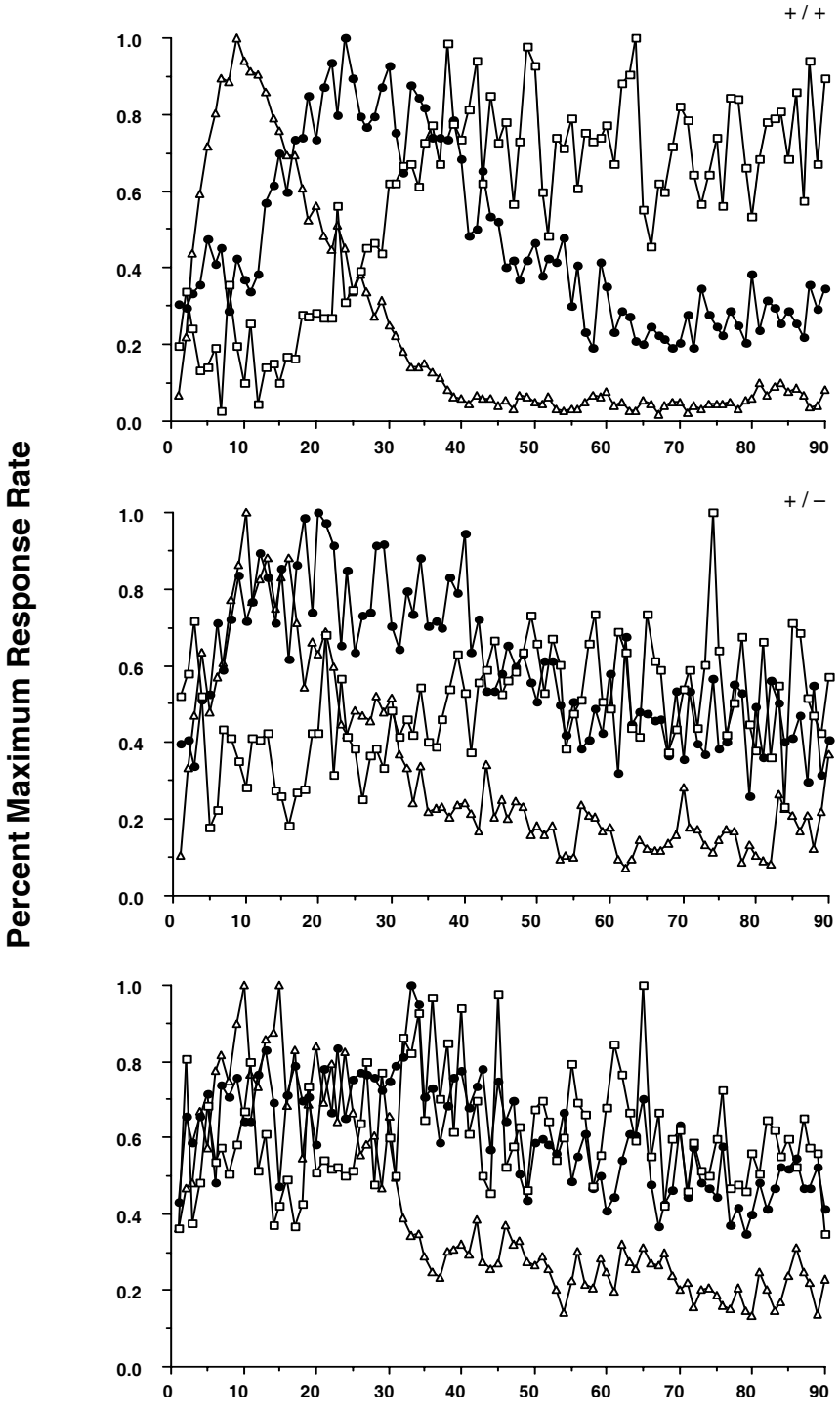

Figure 5. Mean percent maximum response rate as a function of signal duration (s). Data are plotted as a function of responding on each of the three levers: Triangles = 10-s FI/"short" lever; circles = 30-s FI/"intermediate" lever; squares = 90-s FI/"long" lever. Data are plotted as a function of time (s) in each of the FI values for Wild-Type (+/+), Heterozygous (+/-), and Homozygous (-/-) PROT-deficient mice.

Table 1
Peak Time (s), Peak Rate (resp/min), and Spread (s) for the mean response rate functions.

Mouse Type	Peak Time Mean ±SEM	Peak Rate Mean ±SEM	Spread Mean ±SEM
WT – 10s	10.9 ± 0.4	42.3 ± 3.9	15.5 ± 1.6
WT – 30s	29.0 ± 2.0	41.5 ± 2.3	23.0 ± 1.3
WT – 90s		36.5 ± 2.5	31.5 ± 2.5
HT – 10s	12.5 ± 1.3	43.3 ± 3.3	22.0 ± 2.2
HT – 30s	31.5 ± 0.9	42.8 ± 4.2	27.5 ± 1.5
HT – 90s		39.4 ± 3.8	40.3 ± 3.1
HO – 10s	11.1 ± 0.5	38.5 ± 3.4	23.8 ± 1.0
HO – 30s	28.3 ± 2.0	41.0 ± 3.7	35.8 ± 1.1
HO – 90s		34.2 ± 4.6	46.5 ± 2.6

Note: Wild Type = WT (+/+); Heterozygous = HT (+/–); Homozygous = HO (–/–).

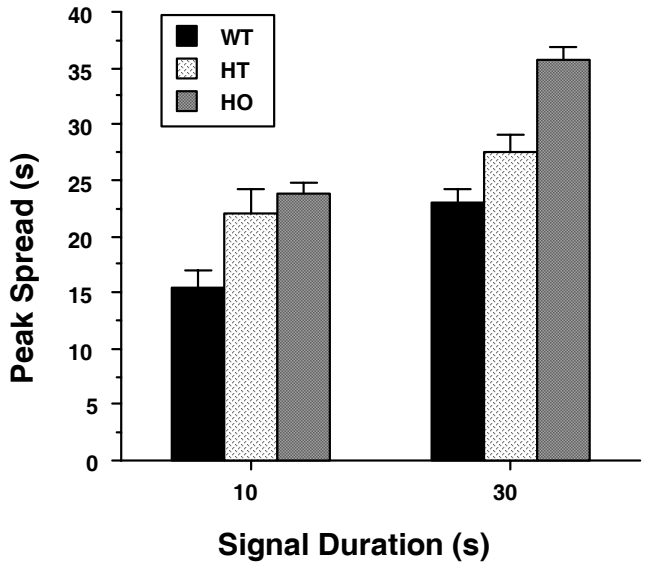

Figure 6. Mean ± standard error of the peak spread (s) for the peak-interval response rate distibutions. Data are plotted as a function of the 10-s and 30-s signal durations for Wild-Type (WT), Heterozygous (HT), and Homozygous (HO) PROT-deficient mice.

Taken together, these data do not indicate any reliable treatment effects on the accuracy of the remembered time of reinforcement or on the levels of motivated

responding for any of the signal durations. What they do indicate is a gene-dosage effect on the precision of interval timing for each of the durations. This is indicated by decrease in the precision of timing as a function of the reduction of the PROT. These findings are consistent with the data obtained from the Morris water-maze test of spatial memory during the probe trials in which the PROT deficient mice performed showed poorer retention of the platform location during the 60-s extinction test. This idea was tested by correlating the number of platform crossings with the spread of the PI functions. These data reveal a significant correlation between the spatial memory and temporal memory measures of performance: $r^2 = 0.796$, as shown in Figure 7.

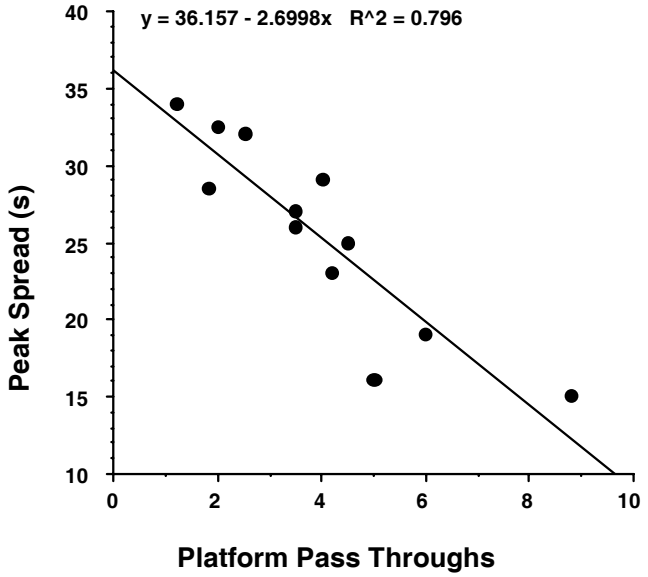

Figure 7. Peak spread (s) obtained from peak-interval training for individual mice plotted as a function of the number of platform pass throughs recorded during the Morris water-maze probe test.The straight line represents the best-fitting regression line through the individual data points.

Additional support for the interpretation of the interval timing data as reflecting a PROT-related decrease in the precision of temporal memory comes from the observed increases in the variance of the *middle* of the high response state and not strictly an increase in the mean and/or variance of the *spread* of the high state as a function of treatment group as shown in Table 2. Analyses of variance showed the treatment effect on the variance for middle, but not spread to be significant: Treatment, $F(2, 6) = 116.12$; Duration, $F(1, 3) = 427.0$; but a nonsignificant Treatment x Duration interaction, $F(2, 6)$ 4.11; and Treatment, $F(2, 6) = 4.51$; Duration, $F(1, 3) = 387.4$; and Treatment x Duration interaction, $F(2, 6) = 2.54$, respectively. This supports memory as being the source of variability in the overall timing performance and not increased variability in response thresholds which might reflect changes in motivational and/or motor components of the task (e.g., Church et al., 1994; Gibbon & Church, 1990, 1992).

Peak time data from the PI testing with gaps plotted as the difference in peak time between trials with and without gaps are shown in Figure 8. The results combined over the two test sessions indicated that wild-type mice perform very similar to rats on peak trials with and without gaps, i.e., they show peak times very

Table 2
Mean (M) and Variance (VAR) of Spread (d) and Middle (m) on non-food probe trials.

Mouse Type	Spread (d) M	Spread (d) Var	Middle (m) M	Middle (m) Var
WT - 10s	13.8	21.1	10.5	6.2
WT - 30s	34.2	74.6	31.0	30.7
HT - 10s	14.3	23.5	10.4	28.5
HT - 30s	35.9	77.1	33.5	90.4
HO - 10s	15.6	26.3	10.7	49.3
HO - 30s	38.6	83.8	31.8	175.6

Note: Wild Type = WT (+/+); Heterozygous = HT (+/–); Homozygous = HO (–/–).

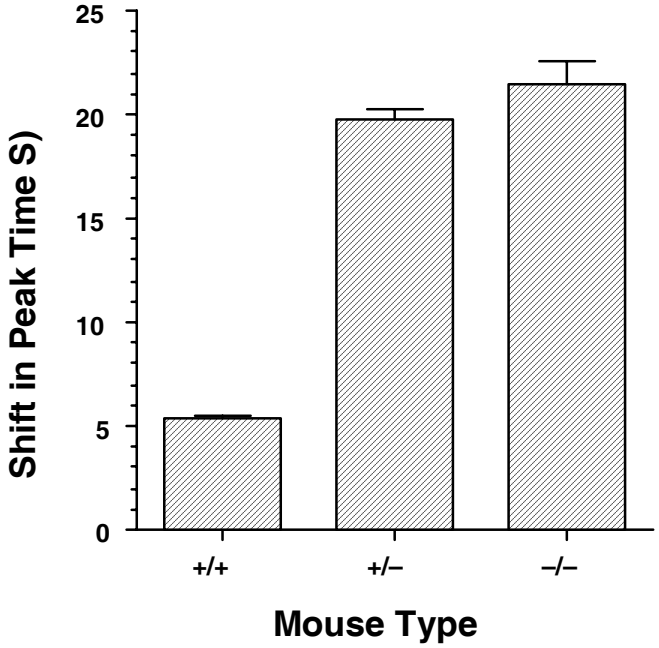

Figure 8. Mean ± standard error of the rightward shift in peak time (s) on 30-s peak-interval trials as a function of the peak time obtained on trials without gaps subtracted from the peak time on trials with 5-s gaps inserted 15-s into the interval. Data are plotted for Wild-Type (+/+), Heterozygous (+/-), and Homozygous (-/-) PROT-deficient mice.

close to the time of reinforcement on trials without gaps and their peak times are shifted to the right about the duration of the 5-s gap on trials with gaps. This result is consistent with mice, like rats, stopping their internal clocks during the gap and resuming timing when the signal comes back on. In contrast, PROT deficient mice (+/- and -/-) show a rightward shift of approximately 20 s, consistent with resetting their clocks following the combined 15-s signal + 5-s gap period. This significant effect of treatment, $F(2, 11) = 156.30$, with +/+ mice significantly different from both +/ - and -/- mice, and no significant difference between +/ - and -/- mice, suggests possible deficiencies in hippocampal function in the PROT-deficient mice because similar resetting of the internal clock has been observed in rats with fimbria-fornix lesions (e.g., Meck et al., 1984). PROT-deficient mice may also have problems in attentional time-sharing that are revealed by the increased salience of the gap or the added processing demands of expecting a break in the signal for these animals (e.g., Buhusi & Meck, 2000, 2002; Buhusi, Paskalis, & Meck, 2002; Buhusi, Sasaki, & Meck, in press; Fortin & Massé, 2000).

In summary, the case has been made here for the value of using interval timing not only to study the psychophysical scaling of stimulus duration, but also to examine the attentional and memory mechanisms involved in temporal discrimination. Interval-timing tasks have previously been shown to be extremely sensitive to pharmacological treatments in normal animals (e.g., Paule et al., 1999). In the current report, interval timing has been shown to as sensitive, if not more so, than commonly used measures of motor behavior (e.g., Rotarod test) and spatial memory (e.g., Morris water-maze) to the behavioral impact of gene knock-out techniques used in the fields of cell and molecular biology as well as neurogenomics. These powerful techniques are also likely to aid our understanding of the brain mechanisms involved in interval timing and to help us answer the question "What makes us tick?"

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Received December 12, 2001.
Revision received June 25, 2002.
Accepted July 2, 2002.