Animal Research Paradigms and Neural Mechanisms of Interval Timing

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Abstract

In exploring the neural mechanisms of interval timing, animal studies can provide more extensive research evidence in pharmacology, molecular biology, single-neuron electrophysiology, and optogenetics compared to research using human subjects. Currently, commonly used animal research paradigms for interval timing include the temporal bisection task, the peak-interval procedure, and differential reinforcement of low rates (DRL), among others. Depending on specific research needs, these paradigms are often modified. The discussion of animal research on interval timing will be organized along two dimensions: (1) introduction and comparison of commonly used animal research paradigms for interval timing; (2) research progress on the neural mechanisms of interval timing based on animal research paradigms, aiming to provide a reference for in-depth psychological research on time perception.

Full Text

Animal Research Paradigms and Related Neural Mechanisms of Interval Timing

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Abstract

In exploring the brain mechanisms of interval timing, animal research offers distinct advantages over human studies by providing more extensive evidence from pharmacology, molecular biology, single-neuron electrophysiology, and optogenetics. Currently, the most commonly used animal research paradigms for

interval timing include the temporal bisection task, peak-interval procedure, and differential reinforcement of low rates. These paradigms are frequently adapted to meet specific research needs. This review examines animal studies of interval timing from two perspectives: (1) an introduction to and comparison of commonly used animal research paradigms for interval timing, and (2) research progress on the neural mechanisms of interval timing based on these paradigms, aiming to provide a reference for future psychological research on time perception.

Keywords: Interval timing; Animal research; Experimental paradigm; Neural mechanism; Time perception

1. Introduction

Time perception is an essential sensory capacity for individual survival, with the perception of intervals ranging from hundreds of milliseconds to several minutes playing a crucial role in various daily behaviors (Buhusi & Meck, 2005). This range of time perception is typically referred to as interval timing. In addition to human studies, numerous researchers have conducted scientific investigations on interval timing using various animal species. Since the 1960s, a substantial body of experimental research has emerged to explore animals' perception of temporal intervals, including the temporal bisection task (Kamada & Hata, 2018; A. Stubbs, 1968), peak-interval procedure (PI) (Roberts, 1981), and differential reinforcement of low rates (DRL) (Sidman, 1956). These experimental paradigms share common principles with frequently used human research methods such as temporal bisection and production tasks. However, because animals cannot provide verbal reports or perform keypress responses, they must learn the required behavioral operations through reinforcement before completing experimental tasks. For example, rats can be trained to press levers or perform nose-pokes to indicate their perception of temporal intervals, with food or water serving as reinforcement rewards.

Compared with human research, animal studies offer several irreplaceable advantages. First, due to ethical considerations, human studies face restrictions on pharmacological research and cannot readily conduct invasive neuronal recordings. In contrast, animal studies—conducted under appropriate ethical guidelines—can employ neuropharmacological, molecular biological, single-neuron recording, and optogenetic techniques to explore specific brain regions, neurotransmitters, and more precise neuronal and molecular mechanisms. For instance, by implanting electrodes in specific brain regions of animals and synchronously recording neuronal activity during interval timing tasks, researchers have identified a unique pattern of neural activity characterized by ramping activity (gradually increasing or decreasing neuronal firing) during timing processes, suggesting that these neurons may participate in temporal processing (Wittmann, 2013). This phenomenon has been observed across multiple species and brain regions, including the posterior parietal cortex of macaques (Leon & Shadlen, 2003) and the medial frontal cortex of rats

(Parker, Chen, Kingyon, Cavanagh, & Narayanan, 2014). The discovery of such neuronal activity supports neural integration models based on earlier human research findings (Wittmann, 2013) and has become important evidence for revealing the brain mechanisms underlying interval timing.

Second, in clinical research, patients typically present with relatively obvious symptoms, making it difficult to conduct longitudinal observations from the early stages of disease development. Animal studies can establish models of neuropsychiatric disorders to explore changes in interval timing throughout disease progression. For example, transgenic mouse studies of Huntington's disease have demonstrated that interval timing can be altered even before the onset of Huntington' s disease symptoms (Orduna, Garcia, Menez, Hong, & Bouzas, 2008). In summary, animal studies of interval timing serve as a powerful complement to human research and contribute to a deeper understanding of the cognitive functions and brain mechanisms of time perception.

This review will first summarize commonly used animal experimental paradigms for interval timing and discuss their applications in interval timing research. Subsequently, it will introduce research progress on neural mechanisms based on these animal interval timing paradigms, with the aim of providing a reference for future psychological research on time perception.

2.1 Temporal Bisection Task

The temporal bisection task is a widely used paradigm in human interval timing research. Typically, participants are first presented with a standard "long" duration stimulus and a standard "short" duration stimulus (such as images or sounds) and are required to remember these two standard durations. They are then asked to judge whether a presented stimulus duration is closer to the standard "short" or "long" duration (Grommet, Hemmes, & Brown, 2019). The principle is identical in animal research. For example, in a 2018 rat study by Kamada and Hata, researchers first conducted extensive conditioning training to teach rats to press a lever for food reinforcement. Subsequently, through conditioning, rats learned to press the lever corresponding to the standard sound duration—pressing the left lever when a standard "short" duration was presented and the right lever when a standard "long" duration was presented, with food rewards provided for correct responses.

After completing this training, rats performed the temporal bisection task, which presented not only the standard "short" and "long" duration sounds but also a series of intermediate durations (in this study: 2 s and 8 s as standards, with intermediate durations of 2.52 s, 3.18 s, 4.00 s, 5.04 s, and 6.35 s). If rats judged the sound as closer to the "short" duration, they pressed the "short" lever; if they judged it as closer to the "long" duration, they pressed the "long" lever. Notably, reinforcement was only provided for judgments of the standard "short" or "long" durations, not for intermediate durations, to maintain reinforcement effectiveness (Kamada & Hata, 2018). Other temporal

bisection studies have used water as reinforcement or nose-poke behavior instead of lever pressing. Both human and animal studies typically include practice sessions with the temporal bisection task until behavior stabilizes before beginning formal experiments.

The primary dependent measure is the proportion of trials in which rats judge each duration as "long,"which is then used for subsequent analysis. In rat studies, 2 s and 8 s are commonly used as the standard "short" and "long" durations, though other durations are employed depending on experimental needs. For example, one study on rat impulsivity used durations ranging from 4 s to 12 s (Marshall, Smith, & Kirkpatrick, 2014). Research indicates that rats can discriminate changes in the hundreds-of-milliseconds range (200–800 ms), but require substantially longer training than for supra-second durations, suggesting that rats may be more sensitive to intervals in the seconds range (Graham, Ho, Bradshaw, & Szabadi, 1994).

In analyzing temporal bisection task results, the point of subjective equality (PSE) is a crucial metric. PSE refers to the duration corresponding to 50% "long" judgments. When a condition' s PSE is significantly lower than the control group' s, it indicates that individuals tend to perceive identical physical durations as longer—i.e., their interval timing is accelerated. Additionally, Weber' s Fraction (WF) can be used to represent temporal sensitivity, with higher WF values indicating lower temporal sensitivity and poorer discrimination between different durations. Thus, the temporal bisection task can be used not only to explore the speed of temporal perception but also to examine individuals' ability to discriminate between different durations.

Rodent studies using the temporal bisection task have frequently explored the mechanisms underlying interval timing and factors that influence it. Cheng and colleagues investigated the effects of intraperitoneal cocaine and ketamine injections on rats performing a temporal bisection task (2 s vs. 8 s). Compared with controls, cocaine significantly reduced PSE, suggesting time overestimation or accelerated interval timing, whereas ketamine did not alter PSE. Previous research has shown that cocaine rapidly increases dopamine levels in both dorsal and ventral striatum, while ketamine significantly increases dopamine in prefrontal cortex, ventral striatum, and hippocampus. These results suggest that alterations in dorsal striatal dopaminergic levels participate in interval timing processing (Cheng, MacDonald, & Meck, 2006).

Human studies have found that emotion can affect interval timing (Droit-Volet, 2013), and rat studies have similarly shown that fear can accelerate interval timing (Faure et al., 2013; Kamada & Hata, 2018). Further research demonstrated that bilateral infusion of the GABA_A receptor agonist muscimol into the basolateral amygdala could counteract the leftward PSE shift induced by fear, indicating that bilateral basolateral amygdala activity is highly associated with fear emotion (Kamada & Hata, 2019).

Researchers have also used the temporal bisection task to examine interval tim-

ing in neuropsychiatric disease states to explore how these conditions affect cognitive behavior and their neural mechanisms. One study established a rat schizophrenia model through maternal immune activation (MIA) and trained rats on a temporal bisection task (2 s vs. 8 s). Results showed that compared with controls, the MIA group had significantly lower PSE, suggesting time overestimation, and significantly higher Weber' s fraction, indicating reduced temporal sensitivity. These findings demonstrate that MIA can impair interval timing in a manner similar to schizophrenia patients (Deane, Millar, Bilkey, & Ward, 2017).

Another study trained transgenic Huntington' s disease (tgHD) rats on a temporal bisection task (2 s vs. 8 s) from 3 to 12 months of age. Results revealed that tgHD rats showed significantly higher Gamma values than wild-type controls as early as 4 months of age. Gamma values in this study were proportional to Weber' s fraction, with larger Gamma values indicating lower temporal sensitivity. Since these rats had not yet exhibited typical HD symptoms, impairments in supra-second interval timing could serve as an early predictive marker for HD progression (Hohn et al., 2011). These results highlight the potential value of the temporal bisection task for investigating neuropsychiatric disease mechanisms and potential clinical applications.

2.2 Peak-Interval Procedure (PI)

The peak-interval procedure is derived from the fixed-interval procedure (FI), which was first used by Skinner in studies of operant conditioning (Hilgard, 1939). In this paradigm, a fixed duration T is established, and a stimulus (e.g., white noise) is presented at the interval onset. Rats can press the lever repeatedly, but only the first press after duration T terminates the sound and yields a reward. Research shows that lever-pressing frequency increases markedly as the interval approaches T, indicating that rats can perceive the passage of time. After reaching T and receiving food reinforcement, rats stop pressing the lever and only gradually increase pressing frequency again.

This paradigm is influenced by numerous factors. One study using the FI paradigm with seven species (including cats, rats, pigeons, and fish) found that animals' accuracy in judging duration T varied depending on the fixed interval used. While animal interval timing is generally thought to conform to Weber' s law, these results conflicted with Weber' s law, suggesting that performance may be limited by species-specific response rates unrelated to timing (Lejeune & Wearden, 1991). Additionally, factors such as reinforcement magnitude and frequency affect FI results (Dews, 1978). Because the FI paradigm relies heavily on reinforcement, it cannot comprehensively or intuitively reflect changes in animals' subjective temporal perception and is currently used primarily in the training phase preceding the peak-interval procedure.

Roberts first proposed the peak-interval procedure and verified that reinforcement magnitude does not affect internal clock rate judgments in this paradigm

(Roberts, 1981). The PI procedure consists of two phases. The first phase is identical to FI: rats receive food rewards for the first lever press after the fixed duration T following stimulus onset. In the second phase, rats perform the PI procedure in which no lever press yields a reward, and the white noise terminates at 2T or 4T. Because rats have practiced the FI procedure, they still expect reward at time T, resulting in increased pressing frequency as T approaches, peaking near T, and decreasing thereafter until stimulus termination. In this phase, FI and PI trials are randomly alternated (50% each) to maintain reinforcement effectiveness.

The primary measure is the peak response rate in PI trials—the maximum frequency of responding (typically lever pressing). The duration corresponding to this peak rate is called peak time, the most important parameter in this paradigm for measuring changes in interval timing (Church, Meck, & Gibbon, 1994). A peak time significantly lower than controls indicates accelerated interval timing, while a significantly higher peak time indicates slowed timing.

The reversed peak-interval procedure (RPI) is a variant of the PI paradigm that uses the intertrial interval (ITI) to study interval timing. While PI examines timing after stimulus onset, RPI examines timing after stimulus offset. In RPI' s first phase (FI phase), rats learn to begin pressing freely after sound termination, with the first press after target duration T triggering sound onset and reward. In the second RPI phase, after sound termination rats press freely, but sound does not reappear until 2T or 4T, without reward. As before, RPI and corresponding FI trials are randomly presented (50% each) to ensure reinforcement effectiveness. Buhusi and Meck used this paradigm to show that ITI length and interference affect working memory and consequently interval timing (Buhusi & Meck, 2006), though their study used light stimuli with rats pressing after light offset.

The mixed fixed-interval schedule (Mixed FI-FI) is another PI variant. Unlike PI, which introduces non-reinforced probe trials, this method introduces a second FI schedule with a different fixed duration T2 (where T2 > T1). The two FI schedules are randomly alternated (50% each). The dependent measure is the response frequency during the second FI (T2). Recent studies have used this paradigm to examine how different reinforcement magnitudes at different durations affect animal timing and to validate various theoretical models of time perception (Blomeley, Lowe, & Wearden, 2004).

The variable interval schedule (VI) is another FI variant where reinforcement is delivered not at a fixed duration T but at intervals averaging T (Herrnstein, 1964). Like FI, VI is combined with PI to study animal interval timing (Matell, Kim, & Hartshorne, 2014).

The peak-interval procedure is widely used in animal interval timing research to explore various factors affecting timing. Swanton and Matell (2011) found that rats showed different timing judgments for auditory and visual stimuli when presented simultaneously, suggesting greater sensitivity to visual stimulus

onset. This indicates that visual and auditory stimuli may affect interval timing through different pathways (Swanton & Matell, 2011). Lejeune and colleagues compared timing perception in 4-month-old juvenile rats and 24-month-old adult rats, finding that adult rats had significantly longer peak times than juveniles, while juveniles' peak times more closely matched the reinforced duration T. This may reflect faster decay of reinforcement memory in adults or delayed perception of stimulus onset and offset (Lejeune, Ferrara, Soffie, Bronchart, & Wearden, 1998). These studies reveal the influences of sensory modality and age on interval timing.

The paradigm is also commonly used in neural mechanism research. Studies have found that dopamine transporter (DAT) gene knockout rats cannot normally control behavioral expression in peak-interval tasks, suggesting an important role for dopaminergic pathways in interval timing (Meck et al., 2012). Other researchers used pharmacological methods to demonstrate that dopamine levels in the nucleus accumbens shell do not affect interval timing in PI tasks (Kurti & Matell, 2011). In that study, microinjections of the dopamine antagonist sulpiride, the dopamine agonist amphetamine, or saline into the nucleus accumbens revealed that while sulpiride reduced response rates, neither drug affected peak time. The PI procedure has also been used to explore theoretical models of interval timing (Buhusi & Meck, 2009). Currently, PI has been less frequently used in neuropsychiatric disease models, though one study examined interval timing in spontaneously hypertensive rats (SHR) to assess the validity of this model for Attention Deficit/Hyperactivity Disorder (ADHD) (Orduna et al., 2008).

2.3 Differential Reinforcement of Low Rates (DRL)

The DRL paradigm is analogous to the temporal production procedure used in human time perception research (Kurti & Matell, 2011). While the production task requires participants to produce a specific duration through keypresses or other actions, the DRL task requires animals to hold a lever press for a specified duration (T) before release to obtain food or water reward; premature release yields no reward. The primary measure is the interval reaction time (IRT)—the duration from lever press to release. The most frequent IRT in formal testing is the peak time, a key indicator of animals' interval timing speed. If an experimental group' s peak time is shorter than controls' , interval timing is accelerated; if longer, timing is slowed.

Skinner' s early research noted that requiring animals to maintain an action for a specified duration to receive food reward could reduce response frequency, a finding confirmed in subsequent studies (Wilson & Keller, 1953). The DRL paradigm is based on this principle. In DRL tasks, animals must control their impulse to release the lever, learning to "wait" and acquire precise timing to obtain rewards. Consequently, the DRL paradigm offers considerable advantages for assessing individual impulsivity. In addition to peak time, DRL also measures non-reinforced responses and impulsive responses, typically defined as

IRTs < 2 seconds. Researchers have also used DRL as an intervention to train temporal precision, reduce impulsive choice, and increase self-control (Eckard & Kyonka, 2018; Smith, Marshall, & Kirkpatrick, 2015).

DRL was the first paradigm to examine animals' perception of their own action durations (Sidman, 1956). It serves as an excellent complement to perception-based paradigms like the temporal bisection task. For example, in the aforementioned study by Cheng et al. (2006), both DRL (12 s) and temporal bisection (2 s vs. 8 s) were used to explore cocaine and ketamine effects on interval timing. DRL results showed that cocaine significantly reduced peak time while ketamine had no effect, consistent with temporal bisection findings and suggesting cocaine accelerates interval timing. Another study examining metabotropic glutamate receptor antagonists used both DRL (18 s) and temporal bisection (2 s vs. 8 s), finding that while the drug increased response and reinforcement rates in DRL, it did not significantly affect peak time or PSE in temporal bisection (Sukhotina et al., 2008).

The paradigm has several variants. The differential reinforcement of long-latency procedure (DRLL) is a DRL variant (Church & Deluty, 1977). While DRL requires animals to maintain a specified action longer than duration T, DRLL requires animals to delay initiating a specified action for longer than T after stimulus onset—for example, waiting duration T after a sound before pressing a lever or nose-poking to obtain reward. Both paradigms study interval timing by examining animals' ability to delay actions (either stopping or initiating), making DRLL an effective interval timing paradigm (Ito, 1981). The tandem fixed ratio-DRL schedule task is a recent variant requiring rats to hold a nose-poke for fixed intervals of 500 ms or 1500 ms after food delivery sound, with successful consecutive holds (typically 1–3) yielding food reward. This study demonstrated rats could accurately estimate 500 ms intervals (Yamaguchi & Sakurai, 2014).

2.4 Free-Operant Psychophysical Procedure (FOPP)

The FOPP paradigm divides stimulus duration (T) into two halves. During training, pressing lever A is reinforced during the first half (1/2T) while lever B is not; during the second half, the contingencies reverse (D. A. Stubbs, 1980). In test trials, animals can freely choose which lever to press, but no reinforcement is provided. Consequently, at stimulus onset, animals press lever A far more frequently than B. As time approaches 1/2T, the probability of pressing B gradually increases, and after 1/2T, B-pressing probability exceeds A-pressing. Animals' lever choices reveal their interval timing. The duration at which animals choose levers A and B with equal probability is the indifferent point; larger indifferent points indicate longer perceived durations and slower interval timing processing.

Some studies have used this paradigm to explore serotonergic pathways' role in interval timing (Body et al., 2006; Body, Kheramin, et al., 2002). Similar

paradigms include the discrete-trials task (Body, Chiang, et al., 2002). In this task, a specific duration T is established. During training, if stimulus duration is less than T, only pressing lever A is reinforced; if greater than T, only lever B is reinforced. Forced-choice trials (presenting only the correct lever) are intermixed to facilitate learning. During testing, animals must judge whether stimulus duration is greater or less than T and press the corresponding lever without reinforcement. Researchers using this paradigm found that the 5-HT2A receptor mediates interval timing alterations induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine (DOI) in mice (Halberstadt et al., 2016).

2.5 Mismatch Negativity (MMN)

Mismatch negativity (MMN) is an event-related potential (ERP) component (Naatanen, Paavilainen, Rinne, & Alho, 2007) that reflects the brain' s detection of novel stimuli. Some researchers have proposed that MMN can also serve as an automatic index of temporal discrimination for studying time perception (Sussman, 2007). MMN can be elicited using an oddball paradigm, which involves inserting rare deviant stimuli among repetitive standard stimuli. By recording ERPs to both stimuli and subtracting the standard from the deviant, MMN is obtained. Deviations can be in stimulus frequency or duration. In auditory MMN research, rhythm changes have also been investigated. MMN can be evoked even without active attention, making it an objective index of sound discrimination accuracy and auditory sensory memory that is not limited by attention and can be recorded under anesthesia or coma (Azabou et al., 2018).

Roger and colleagues presented freely moving rats with repetitive fixed-duration sounds as standard stimuli, occasionally inserting shorter sounds as deviants (standard: 150 ms; deviants: 125, 100, 75, and 50 ms). EEG electrodes implanted in primary motor cortex, parietal cortex, and anterior cingulate cortex recorded neural activity. Results showed that all deviants except 125 ms elicited MMN, with the smallest detectable duration difference threshold being approximately 16–33% of the standard duration (Roger, Hasbroucq, Rabat, Vidal, & Burle, 2009). Recently, researchers using anesthetized mice found MMN elicited by different durations (Lipponen et al., 2019). In future research, MMN may represent an important direction for interval timing studies.

2.6 Recording Observation Method

The recording observation method is typically used to observe animals' natural behaviors. Rather than training animals to perform specific operations, these studies simulate natural behaviors in laboratory settings and analyze behavioral timing from video recordings to understand animals' time perception. This approach can examine interval timing related to daily activities, such as food protection behavior in rats. Research has shown that amphetamine increased food-protecting rats'avoidance of potential competitors by 31.08%, while haloperidol decreased avoidance time by 35.63% (Wallace, Wallace, Field, &

Whishaw, 2006). Another study used this method to examine the contribution of the dorsocentral striatum (DCS) to temporal information processing (in the range of seconds to minutes) by unilaterally lesioning DCS in Long-Evans rats and conducting food protection tasks. Generally, if rats perceive longer eating times, they adopt lateral dodging while holding food in their mouths (dodge behavior); if they perceive shorter durations, they tend to use turning avoidance (bracing behavior). Normal rats transition from dodge to bracing behavior after an average of 3 trials, whereas DCS-lesioned rats require 5 trials, reflecting altered subjective time perception. This study suggests DCS may be a key structure affecting individual interval timing information (Blankenship, Cheatwood, & Wallace, 2017). With advances in animal behavior analysis technology, this method' s advantages are becoming more apparent, as it allows more direct examination of how interval timing affects animals' daily behaviors and their underlying mechanisms.

2.7 Comparison of Animal Interval Timing Research Paradigms

Researchers have designed numerous interval timing paradigms for different experimental purposes and conditions. The six categories described above represent the most common types in animal interval timing research, with their summary and comparison presented in Table 1 .

The temporal bisection task is widely used to explore factors affecting interval timing speed and temporal sensitivity, such as emotion, drugs, and neuropsychiatric diseases. However, it requires only binary "short" vs. "long" judgments rather than direct duration estimation—a limitation addressed by peak-interval and DRL paradigms. In PI paradigms, animals increase lever-pressing frequency near the target duration, while DRL paradigms require animals to hold lever presses until the target duration or wait before pressing, both reflecting animals' estimation of specific durations. Consequently, recent studies often combine these paradigms with neuronal recording techniques to explore neural coding patterns during target duration estimation (Mello, Soares, & Paton, 2015; Parker, Ruggiero, & Narayanan, 2015). Compared to PI, where animals repeatedly press levers (creating substantial motor artifacts for neuronal recordings), DRL tasks involve minimal or maintained behavior during waiting periods, making them more suitable for analyzing and identifying neurons that encode interval timing. Indeed, studies using 12-s DRL have identified ramping responses in rat medial frontal cortex that represent temporal processing during the timing interval (Parker et al., 2014). However, DRL paradigms are more susceptible to individual impulsivity.

The free-operant psychophysical procedure requires animals to judge whether stimulus duration is greater or less than 1/2 the standard duration. This paradigm allows freer operant behavior, as lever pressing is not cued by external stimuli and correct presses during training are always reinforced. FOPP is also used to examine duration estimation and discrimination. Compared to tempo-

ral bisection, FOPP permits faster operant behavior and yields more data per trial, making it suitable for longer durations (e.g., 50 s or 150 s). However, the free-operant mode may introduce confounds—during testing, animals might rely on memory of previous lever-press sequences rather than duration estimation (D. A. Stubbs, 1980).

In contrast to the long-term reinforcement training required by behavioral paradigms, mismatch negativity provides a more automatic index unaffected by attention, enabling studies in anesthetized animals. However, MMN typically compares sub-second timing and involves pre-attentive processing, so its underlying mechanisms may differ from those of the aforementioned paradigms. The recording observation method better examines natural daily behaviors but currently offers limited quantifiable behaviors, requiring further exploration.

Table 1 Comparison of Animal Research Paradigms for Interval Timing

Paradigm	Main Parameters	Advantages	Disadvantages/Limitations
Temporal Bisection Task	Point of Subjective Equality (PSE), Weber' s Fraction	Better for examining temporal sensitivity; widely used for exploring factors affecting timing speed and sensitivity	Requires binary judgment rather than direct duration estimation
Peak-Interval Procedure	Peak time, peak response rate	More naturalistic; animals can subjectively judge durations; less motor constraint; suitable for neuronal recording	Repeated lever pressing may introduce motor artifacts in neuronal recordings

Paradigm	Main Parameters	Advantages	Disadvantages/Limitations
Differential Reinforcement of Low Rates	Peak time, impulsive responses, non-reinforced responses	Closer to human production methods; requires waiting for specific durations	More susceptible to individual impulsivity
Free-Operant Psychophysical Procedure	Indifferent point	Fast operant behavior; suitable for long-duration studies	Free operant behavior may introduce confounds (e.g., sequential memory)
Mismatch Negativity	Amplitude and latency	Automatic processing; not attention-dependent; can study anesthetized animals	Limited time window; sub-second durations; pre-attentive mechanisms may differ
Recording Observation Method	Duration of specific behaviors	Naturalistic behavior; no training effects; examines daily behavior timing	Limited quantifiable behaviors currently available

3. Neural Mechanisms of Interval Timing: Evidence from Animal Experimental Paradigms

Selecting appropriate paradigms or adapting existing ones to experimental goals and conditions is crucial for effectively exploring the neural mechanisms of interval timing. The three major paradigms—temporal bisection, peak-interval procedure, and differential reinforcement of low rates—are widely used in animal studies of interval timing neural mechanisms. In recent years, combining these animal paradigms with rich neurobiological methods has yielded substantial experimental evidence on brain mechanisms closely related to interval timing processing, providing powerful supplementation to human research findings. This section will focus on neural circuits and neurotransmitters, introducing

research progress on interval timing neural mechanisms based on the aforementioned animal paradigms.

3.1 Neural Circuit Mechanisms of Interval Timing

Early researchers tended to believe that the basal ganglia housed the internal clock (Meck, 1996). However, accumulating evidence has led to the view that interval timing involves broader neural network participation (Matell & Meck, 2004), including the substantia nigra and striatum of the basal ganglia, cortical regions such as the medial prefrontal cortex, and hippocampal structures.

Using simultaneous multi-site single-neuron recording, researchers recorded dorsolateral striatum and dorsomedial prefrontal cortex in rats performing a mixed fixed-interval schedule (10 s, 40 s). Results showed that individual neurons in dorsolateral striatum could encode duration through slowly changing firing rates, while a minority of striatal and cortical neurons could discriminate durations as a population (Matell, Meck, & Nicolelis, 2003). Another study trained rats on a series of FI tasks (12–60 s) while recording striatal neurons. Results demonstrated that decoding striatal neuronal activity could predict timing behavior when animals performed new duration tasks, and striatal disruption interfered with timing behavior, further confirming striatal encoding of interval timing (Mello et al., 2015). Using optogenetics, researchers examined the role of substantia nigra in temporal processing (Toda et al., 2017). This head-fixed mouse study used a novel PI-like paradigm based on licking behavior. Results showed that optogenetic stimulation of GABAergic projections from substantia nigra pars reticulata to superior colliculus could temporarily stop licking and delay the onset of exploratory licking in subsequent trials without affecting licking duration. The authors proposed that nigrotectal projections may have motor control functions that also influence timing, possibly because blocking this pathway allows more information to reach cortex via nigrothalamic pathways, thereby affecting interval timing.

Kim and colleagues found that inactivating medial prefrontal cortex (mPFC) via GABA receptor agonist injection significantly impaired rats' temporal bisection performance (J. Kim, Jung, Byun, Jo, & Jung, 2009). In subsequent research, they recorded mPFC neuronal activity during temporal bisection and found that mPFC neuronal ensembles conveyed precise information about elapsed time, suggesting that mPFC possesses clock-like functions (J. Kim, Ghim, Lee, & Jung, 2013). Additionally, in a tandem fixed ratio–DRL task requiring rats to maintain nose-poking for 1.5 s or 2.5 s, researchers recorded medial prefrontal cortex activity and found many mPFC neurons showed sustained spiking during timing. Temporarily suspending mPFC activity via local cooling delayed rats' departure from the nose-poke waiting area, reflecting prolonged duration estimation (Xu, Zhang, Dan, & Poo, 2014), further confirming mPFC involvement in interval timing.

The hippocampus, as a crucial memory-related structure, plays an important

role in interval timing (Oprisan, Aft, Buhusi, & Buhusi, 2018). Hippocampal lesion studies have confirmed this view (Meck, Church, & Matell, 2013). For example, in a 12-s DRL task, hippocampal lesions shortened peak time, reflecting underestimation of the target duration (Jaldow & Oakley, 1990). In a PI task, dorsal hippocampal lesions caused underestimation of a 15-s duration (Tam, Jennings, & Bonardi, 2013). Some researchers have proposed that the hippocampus may contain time cells that store temporal memory information (Eichenbaum, 2014). However, compared to basal ganglia and cortical regions, the hippocampus' s influence on interval timing appears less direct, likely affecting timing through memory mechanisms. Its specific mechanisms and relationships with other brain regions require further precise investigation.

Animal interval timing studies have confirmed the striatum' s central role in timing processes and revealed that coordinated changes in striatal and cortical neuronal activity encode timing behavior. According to the striatal beat frequency (SBF) model, the striatum likely times intervals by detecting changes in cortical oscillatory activity, while nigrostriatal dopaminergic projections may modulate timing (Matell & Meck, 2004). Toda et al.' s optogenetics study provides an alternative explanation, suggesting that altered GABAergic projections from substantia nigra pars reticulata to thalamus may affect cortical activity, which the striatum detects and uses to influence timing. Increasing evidence supports the role of prefrontal cortex in timing. Some mPFC neurons convey timing information by modulating firing rates, though mPFC activity during timing is more complex than striatal activity, potentially also encoding motor planning and reward expectation (Xu et al., 2014). Additionally, mPFC participates in attentional control and working memory modulation (J. Kim et al., 2009), which also affect interval timing, suggesting multifaceted mechanisms. Some striatal and mPFC neurons exhibit ramping activity during interval timing, with firing patterns that match current durations. The ramping activity model proposes that the brain computes time by integrating this activity (Hass & Durstewitz, 2016; Xu et al., 2014). Animal studies have also confirmed hippocampal involvement in interval timing. Duration judgments require comparing current intervals with stored memories, so as a key memory-encoding region, the hippocampus likely influences timing through memory storage. Since the transmission and processing of current timing information remain unclear, interpretations of each brain region' s role are often based on existing theoretical models. Accumulating experimental evidence will help reveal the true processes of interval timing.

3.2 Role of Neurotransmitters in Interval Timing Neural Circuits

Research has identified several neurotransmitters involved in interval timing processing, including dopamine, serotonin (5-HT), acetylcholine, glutamate, and GABA, which likely participate in transmitting interval timing information between brain regions.

The striatal dopaminergic pathway is widely believed to be related to the rate of the internal clock and represents an important neural substrate for interval timing (Jones & Jahanshahi, 2009). Recent research found that in a 6-s PI task, blocking D1 and D2 receptors in dorsomedial striatum delayed nose-poke termination, while blocking D2 receptors in both dorsolateral and dorsomedial striatum delayed nose-poke initiation. This suggests striatal dopamine levels may regulate both the start and stop functions of timing (De Corte, Wagner, Matell, & Narayanan, 2019). Substantia nigra lesions (via local 6-OHDA injection) impair interval timing in PI tasks, while intraperitoneal L-DOPA (a dopamine precursor) administration can restore normal timing (Meck, 2006), suggesting nigral dopaminergic pathways also participate in interval timing. Parker and colleagues trained rats on a timing task (waiting 12 s before lever pressing, equivalent to DRLL) while recording medial frontal cortex (MFC) activity and locally administering the D1 dopamine receptor (D1DR) agonist SKF82958. This drug disrupted interval timing behavior and reduced ramping neural activity representing timing processing (Parker et al., 2015), indicating MFC neuronal encoding of interval timing is modulated by dopamine levels.

In further research, Kim and colleagues trained mice with dopamine depletion from 6-OHDA injection in the ventral tegmental area (VTA) on a 12-s timing task (equivalent to DRLL) while recording MFC activity. VTA dopamine depletion reduced delta-frequency neural activity in MFC during timing. Optogenetic stimulation of D1DR+ neurons in MFC increased ramping activity, and stimulating MFC-D1DR+ neurons at delta frequency (2 Hz) compensated for timing deficits caused by VTA dopamine depletion (Y. C. Kim et al., 2017). Thus, VTA-to-MFC dopaminergic projections participate in interval timing. In subsequent work specifically recording MFC D1DR+ neurons, Kim and Narayanan found these neurons exhibited early ramping responses during timing intervals, and early stimulation of MFC D1DR+ neurons could compensate for timing deficits caused by midbrain dopamine depletion (Y. C. Kim & Narayanan, 2019). These results clearly demonstrate that midbrain dopaminergic projections modulate interval timing by influencing MFC D1DR+ neurons.

Meck and colleagues also examined cholinergic pathways' effects on interval timing (using a 20-s PI paradigm). They found that the cholinergic antagonist atropine impaired temporal discrimination and right-shifted peak time, suggesting the cholinergic system may affect the storage speed of temporal memory in timing tasks (Meck, 1996; Meck & Church, 1987). Other research found that maternal dietary choline supplementation could enhance offspring' s interval timing ability and temporal memory (Cheng, Scott, Penney, Williams, & Meck, 2008). In that study, choline was supplemented in maternal diet during embryonic days 12–17, and offspring were tested on temporal bisection (2 s vs. 8 s, auditory and visual signals) in adulthood. Prenatal choline supplementation significantly improved offspring rats' sensitivity to target durations. Some researchers propose that altered cholinergic levels may affect how striatal interneurons modulate medium spiny neurons, thereby influencing interval timing (Coull, Cheng, & Meck, 2011). Daniels et al. (2015) found that in rats

performing a compound FI task, injection of mecamylamine (an acetylcholine receptor antagonist) rapidly restored normal interval timing in nicotine-treated rats (nicotine being a cholinergic agonist that disrupts timing), suggesting acetylcholine receptors may mediate nicotine' s timing disruption.

Research on 5-HT, glutamate, and GABA in interval timing is relatively limited. Some studies found that the 5-HT2A/2C agonist DOI reduced rats' temporal discrimination in discrete-trials tasks, while selective 5-HT2A antagonists blocked this effect (Body et al., 2006; Body, Chiang, et al., 2002; Halberstadt et al., 2016). However, these studies used systemic drug administration, leaving the neural mechanisms unclear. Hata proposed that glutamate may be important for interval timing (Hata, 2011), as corticostriatal projections are primarily glutamatergic (Matell & Meck, 2004), but specific mechanisms remain poorly understood. One PI study found that the NMDA receptor antagonist MK-801 affected interval timing, but systemic injection precluded mechanistic conclusions. Toda et al. used optogenetics to confirm that GABAergic projections from substantia nigra pars reticulata affect timing behavior (Toda et al., 2017), though specific mechanisms require further investigation.

In the interval timing neural network, dopaminergic pathways play crucial modulatory roles. Extensive research confirms that VTA-to-cortex and substantia nigra pars compacta-to-striatum dopaminergic projections are important for interval timing. VTA-to-cortex projections may modulate timing by synchronizing cortical activity or influencing cortical ramping activity patterns, while nigral dopaminergic projections to striatum may modulate synaptic strength onto medium spiny neurons (MSNs), representing a key mechanism for regulating striatal timing (Matell & Meck, 2004). Early cholinergic research focused on memory storage speed, but recent striatal microcircuit studies suggest alternative mechanisms. In this microcircuit, tonically active neurons (TANs) transmit cholinergic signals to fast-spiking interneurons (FSIs), which then inhibit timing-critical MSNs via GABAergic projections (Coull et al., 2011). Thus, the cholinergic system may modulate timing through the TAN-FSI-MSN circuit, where GABA also plays an important role as an inhibitory neurotransmitter. However, 5-HT, GABA, and glutamate are widely distributed in the central nervous system and may act in more complex, less specific ways. Future studies require more refined experimental designs to explore these neurotransmitters' mechanisms in interval timing networks.

4. Summary and Outlook

In summary, researchers have provided substantial evidence for exploring interval timing brain mechanisms through various neurobiological methods (lesions, neuronal recordings, optogenetics, etc.). Animal research paradigms have been essential in this process. Currently, the most commonly used animal paradigms are temporal bisection, peak-interval procedure, differential reinforcement of low rates, and free-operant psychophysical procedure. While all can reflect the speed of interval estimation, they have different emphases: temporal bisection better

captures temporal sensitivity; peak-interval and DRL paradigms better reflect subjective duration estimation, with DRL being closer to human production methods; and free-operant psychophysical procedure' s rapid operant behavior makes it suitable for longer durations. Additionally, some methods require no prior behavioral training, including mismatch negativity and recording observation. MMN is suitable for exploring automatic, attention-independent timing, while recording observation can examine naturalistic duration estimation. Selecting appropriate paradigms or developing new ones according to experimental needs will facilitate exploration of interval timing mechanisms.

Current animal research has confirmed that dopamine receptor-positive neurons in medial frontal cortex encode timing behavior (Parker et al., 2015) and that this encoding is influenced by VTA dopaminergic projections (Y. C. Kim et al., 2017). Beyond dopaminergic circuits, acetylcholine may primarily affect temporal memory storage speed (Meck, 1996), while 5-HT (Halberstadt et al., 2016), glutamate (Hata, 2011), and GABA (Toda et al., 2017) likely participate in temporal information transmission, though evidence remains limited and nonspecific. Future research should further examine how brain regions encode interval timing and how neurotransmitters transmit timing information between regions, while also leveraging animal research advantages to explore additional perspectives.

Nowak et al. (2016) proposed that MMN changes could serve as an early marker for age-related interval timing decline in humans. Animal studies could longitudinally record MMN changes in the same animals throughout aging to explore dynamic timing changes and mechanisms. Other researchers have analyzed how genetic polymorphisms in neurotransmitter-related and clock genes affect time perception (Marinho et al., 2018), finding associations with multiple behavioral phenotypes. Transgenic animals could help explore target genes' roles in interval timing. Cross-modal timing research also offers new insights. Studies have shown that under specific conditions, auditory stimuli can distort visual interval timing, likely through cross-modal integration rather than arousal changes (Asaoka & Gyoba, 2016). Developing cross-modal timing paradigms in animals combined with electrophysiological recordings could help investigate cross-modal integration mechanisms.

Interval timing is altered in some neuropsychiatric diseases, even appearing early in disease progression. Huntington's disease animal model research confirms that interval timing changes precede symptom onset (Hohn et al., 2011), and recent human studies suggest supra-second timing deficits may serve as early markers for Parkinson' s disease (Bernardinis, Atashzar, Jog, & Patel, 2019). These findings suggest interval timing could aid early disease identification. Using neuropsychiatric disease model animals with interval timing paradigms could explore timing changes during disease development and treatment, evaluating their potential as biomarkers while revealing neural mechanisms. Studies have already examined interval timing in Huntington' s disease (Garces et al., 2018) and schizophrenia models (Deane et al., 2017). Future research could extend to

depression, pain, and autism.

A 2015 meta-analysis by Thönes and Oberfeld confirmed moderate effects of depression on subjective time flow and interval timing (Thones & Oberfeld, 2015). Numerous studies have explored pain' s effects on interval timing, showing that cold pressor pain prolongs interval timing in humans performing temporal bisection (Rey et al., 2017), a phenomenon recently confirmed in acute inflammatory pain model rats (Liu, Wang, Wang, & Luo, 2019). However, more pain models and paradigms are needed to verify this and reveal mechanisms. With rising incidence, autism research is gaining attention. Studies have confirmed timing differences between autism spectrum and neurotypical individuals (Doenyas, Mutluer, Genc, & Balci, 2019; Jurek et al., 2019), though mechanisms remain unclear. Animal models of depression, pain, or autism combined with interval timing paradigms could help reveal these diseases' mechanisms and their effects on cognitive processing.

Information processing and modeling of interval timing remain hot topics with substantial controversy. The pacemaker-accumulator (PA) model, based on scalar timing theory (Gibbon, Church, & Meck, 1984), proposes specific brain regions encode interval timing. The striatal beat frequency (SBF) model (Meck, Penney, & Pouthas, 2008), derived from PA, suggests interval timing involves broader networks including striatum and cortex. State-dependent network models propose that interval timing depends on repeatable dynamic changes in neural and synaptic properties throughout the brain (Buonomano, 2000) rather than specific mechanisms. Some studies have compared these models—for example, Kleinmann et al. (2016) used a modified mixed fixed-interval procedure in macaques and found that both traditional PA and state-dependent network models require modification to explain results. Hass and Durstewitz (2016) reviewed current timing models, suggesting that interval judgments may be an inherent property or "byproduct" of information processing across multiple brain regions, with temporal information from different modalities integrated in Bayesian optimal fashion in specific timing centers (e.g., prefrontal cortex and striatum). Animal research has provided crucial support for these models, with neuronal recording and optogenetics providing extensive evidence for the roles of prefrontal cortex, striatum, and VTA in timing and their circuit mechanisms (De Corte et al., 2019; Y. C. Kim et al., 2017). Neuronal ramping responses found across multiple brain regions strongly support neural integration models (Wittmann, 2013). Future animal studies could simultaneously record neural coding patterns across multiple brain regions during interval timing to analyze inter-regional information exchange and explore timing circuits holistically (e.g., corticostriatal and corticocerebellar circuits; Coull et al., 2011), while conducting more synaptic- and molecular-level studies integrated with computational neuroscience to develop more accurate interval timing information processing models.

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