Mice Can Monitor Their Timing Errors

By

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Abstract

The ability to accurately monitor the passage of time is pivotal for many functions such as associative learning and planning. Earlier experiments show that humans and rats can integrate their representational (endogenous) uncertainty about time intervals into decisions in a nearly normative fashion, suggesting that they can monitor their timing errors. This ability can be formalized as knowing whether and how much one has under- or over-estimated the duration of an event without any feedback, which we refer to as metric error monitoring (MEM). Although MEM has been documented in humans and very recently in rats (with two-alternative two choice procedure), whether mice can monitor their timing errors based on confidence-like measures is unknown. I tested this hypothesis in C57BL/6 male mice (N=16). Mice were trained to depress a lever for a minimum target duration in order to receive a reward in the food hopper. No reward was given when mice under-produced the minimum required target interval. During test trials, the rate of nose-pokes into the food hopper during a variable response window after releasing the lever was recorded. Mice nose-poked more vigorously (reflecting higher reward expectancy) following temporal productions around the target duration compared to when they under-produced the minimum target interval. This result suggests that mice judge whether or not their temporal production was close to meeting the task criterion to receive a reward, and thus show temporal error monitoring abilities in mice. Our findings also provide the necessary behavioral tool to study the neural basis based on correlational and manipulative methods in non-human animals.

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To all those mentioned above, as well as the countless others who have supported me in various ways, I extend my deepest gratitude for their exceptional contributions to this thesis and my academic journey.

Dedication

With heartfelt appreciation, I dedicate this thesis to my amazing friends and supportive family. Their unconditional love, support, and encouragement has been my foundation throughout this endeavor.

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List of Abbreviations

μ	Mean
2AFC	Two-alternative forced-choice
AAV	Adeno associated virus
ACC	Anterior cingulate cortex
ASD	Autism spectrum disorder
CDF	Cumulative distribution function
CPAM	Creelman's pacemaker accumulator model
CRN	Correct-related negativity
DAergic	Dopaminergic
dACC	Dorsal anterior cingulate cortex
DMTS	Delayed match-to-sample
DRRD	Differential reinforcement of response duration
DRL	Differential reinforcement of low rates of responding
EEG	Electroencephalography
ERN	Error-related negativity
ERP	Event related potential
EVC	Expected value of control
FI	Fixed interval
FOJ	First order judgement
ITI	Intertrial interval
IVC	Individually ventilated cages

LME	Linear mixed effects
MEG	Magnetoencephalography
MEM	Metric error monitoring
MFB	Medial forebrain bundle
ML	Maximum likelihood
NAc	Nucleus accumbens
OCD	Obsessive compulsive disorder
PDF	Probability density function
Pe	Error-related positivity
PFC	Prefrontal cortex
PI	Peak interval
SBF	Striatal beat frequency model
SD	Standard deviation
SET	Scalar expectancy theory
SN	Substantia nigra
SOJ	Second order judgement
T	Target duration
TD	Typically developing
TEM	Temporal error monitoring
TP	Temporal production
TPAM	Treisman's pacemaker accumulator model
VTA	Ventral tegmental area

Chapter 1: Literature Review

1.1: Importance of Timing

The ability to keep track of elapsing time plays a pivotal role in various aspects of our lives. It influences everything from our motor skills and coordination (Buhisi & Meck, 2005) to learning (Gallistel & Gibbon, 2000), where the ability to accurately estimate the duration of events aids in the formation of temporal associations. Additionally, our perception (Fraisse, 1984), attention (Nobre, 2018), and decision-making (Balci et al., 2011) skills are intricately linked to our temporal processing capabilities. For instance, our perception of the duration of stimuli or events can influence how we adaptively and dynamically allocate our attention to events in our environment (Akdoğan, van Rijn & Balci, 2016). Timing is also relevant to everyday situations such as arranging transportation, where precise timing ensures arrival at the right moment. The same applies to coordinating movements in activities like playing an instrument, typing, or in speech generation (Buhisi & Meck, 2005) for clear communication. These examples highlight the indispensability of temporal information processing in our daily lives.

Temporal information is processed and utilized across different timescales (see Figure 1). For instance, the circadian timing system operates on a ~24-hour cycle to regulate crucial functions such as sleep, metabolism, and reproduction. It functions as an internal clock, generating a rhythm that is not cognitively penetrable and thus cannot be arbitrarily controlled (Okamura et al., 2002). For instance, when traveling across different time zones, one cannot consciously adjust to the new day/night cycle to overcome the adverse effects of "jet lag." At the other end of the temporal spectrum, the brain can also time very brief intervals in the

millisecond range, which is essential for everyday activities such as speech recognition and production, motor control, and coordination.

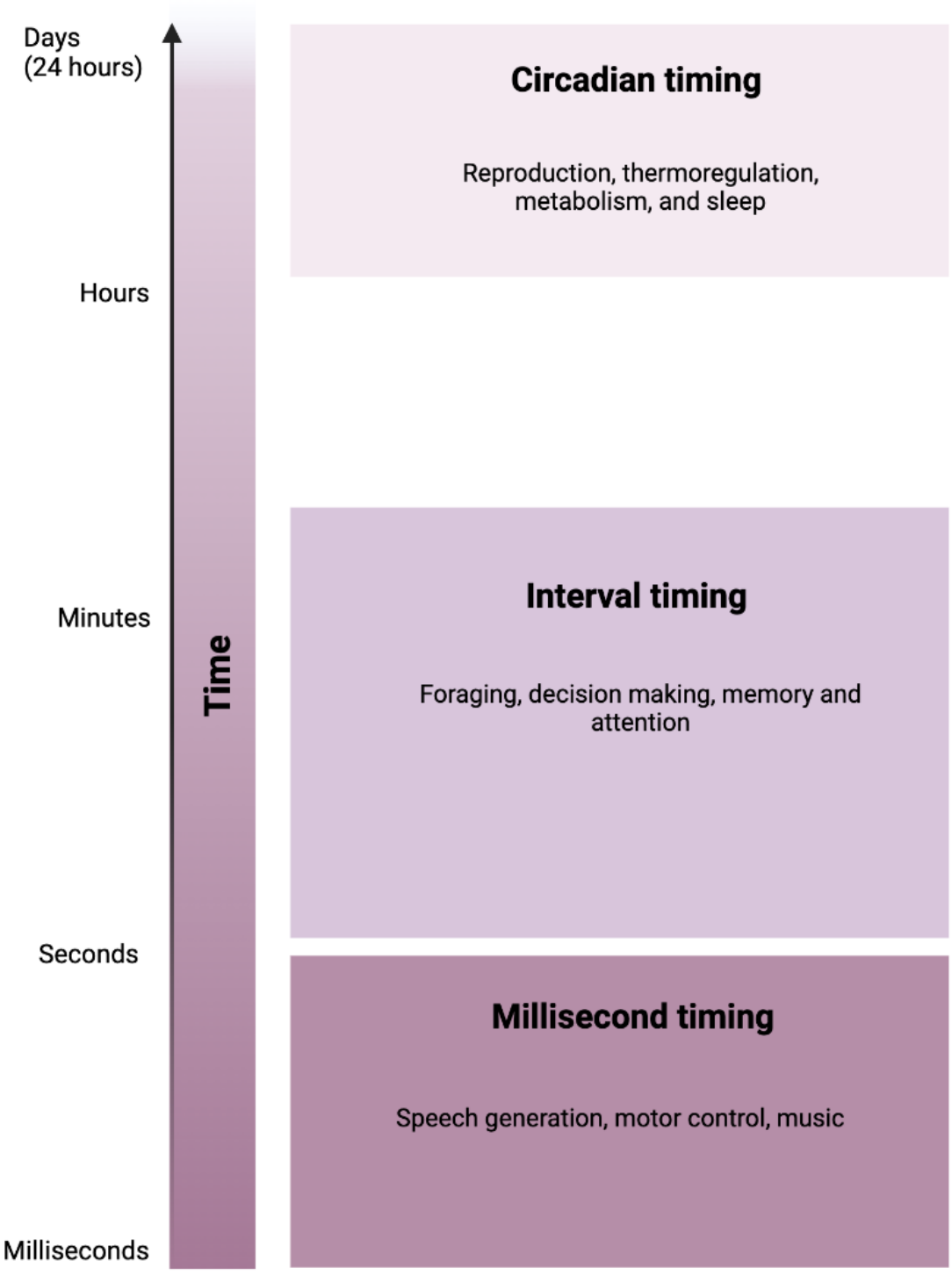


Figure 1: A schematic showing the different timescales seen in humans and animals highlighting the important behavioural components of each timescale. (Designed on biorender.com)

1.2: Interval timing

This thesis focuses on interval timing, specifically exploring how non-human animals can track errors during timing. Interval timing is a timescale that pertains to estimating and reproducing durations in the seconds-to-minutes range which relies on a number of other cognitive processes. One of the cognitive processes involved with interval timing is memory (Gibbon et al., 1984). When estimating durations, individuals draw upon their memory to recall previous experiences and compare them with the current interval. Memory helps establish a temporal reference point and enables individuals to make relative judgments about whether the current duration is shorter or longer than their prior experience. Attentional processes are also critical in interval timing (Gibbon et al., 1984; Meck et al., 2013). Individuals need to allocate and sustain their attention to the ongoing event or the passage of time in order to estimate the duration accurately. Furthermore, interval timing is intricately connected to decision-making processes (Balci et al., 2011). When faced with temporal tasks, individuals need to make decisions about the duration of events, the timing of actions, and the allocation of attentional resources. Decisions are influenced by the subjective time.

1.2.1: The neural basis of interval timing

Several brain regions have been implicated in the neural basis of interval timing, with particular emphasis on the role of the basal ganglia and striatum (Matell & Meck, 2000, 2004; Meck & Benson, 2002), prefrontal cortex (e.g., Macar et al., 2002; Lewis & Miall, 2003), and cerebellum (e.g., Ivry et al., 2002). This anatomical arrangement produces a

cortico-striatal-thalamic-cortical loop, the pathway that is proposed to underlie the necessary computations for the timing of behavior.

The basal ganglia, a set of subcortical brain nuclei, are involved in a variety of cognitive and motivational processes (Graybiel, 1997; Middleton & Strick, 1994; Lawrence et al., 1998) and appear to be critical for interval timing. Excitatory input from the cortex to the basal ganglia comes primarily into the striatum, the input nucleus of the basal ganglia. The dorsal striatum also receives modulatory dopaminergic input from the substantia nigra pars compacta (SNPC), one of the midbrain dopamine nuclei. Lesions of the dorsal striatum or SNPC in the rat eliminate the ability to perform timing tasks (Meck, 2006).

Both animal and human studies have provided insights into the crucial functions of the medial prefrontal cortex (mPFC) in various cognitive processes. The mPFC has been implicated in attentional processes (e.g., Arnsten, 2009; Paneri & Gregoriou, 2017), working memory (e.g., Funahashi, 2017; Murray et al., 2017; Spaak et al., 2017), as well as higher-order functions like planning and decision making (e.g., Dixon & Christoff, 2014). Since timing is essential for effective planning and decision-making (Buhusi and Meck, 2005; Meck et al., 2012; Bermudez and Schultz, 2014; Finnerty et al., 2015; Kirkpatrick and Balsam, 2016), numerous studies have investigated mPFC in relation to the perception, encoding, and processing of time intervals. Research involving lesion studies has explored the involvement of the mPFC in memory for duration (Jackson et al., 1998) and has shown initial impairments in the acquisition of timed responses, which could be overcome through extensive training (Dietrich and Allen, 1998). Furthermore, investigations utilizing pharmacological inactivation of the mPFC (Kim et al., 2009) or electrophysiological recordings of mPFC neurons (Kim et al., 2013) in temporal bisection tasks

have suggested the participation of the mPFC in discriminating between different time durations. Notably, alterations in the firing patterns of mPFC neurons have been observed during the performance of timed behaviors (Niki and Watanabe, 1979; Xu et al., 2014).

The cerebellum is traditionally associated with motor coordination and motor learning (Doyon, 1997), but has also been recognized as an important player in interval timing processes. Emerging evidence suggests that the cerebellum contributes significantly to temporal processing and plays a role in the perception and production of time intervals. Studies usinganimal models and human neuroimaging have provided insights into the involvement of the cerebellum in interval timing. Lesion studies in animals have shown impairments in temporal discrimination and timing accuracy following cerebellar damage (Ivry et al., 2002). One proposed role of the cerebellum in interval timing is its contribution to the generation and maintenance of an internal timing signal, often referred to as an "internal clock" or "pacemaker." The cerebellum is thought to interact with other brain regions involved in timing, such as the basal ganglia and prefrontal cortex, to regulate the speed and accuracy of timing processes (Ivry and Spencer, 2004; Spencer et al., 2003).

1.2.2: The role of dopamine in interval timing

Studies that have investigated interval timing highlight the crucial role of dopaminergic activity, and research has shown that manipulating the dopamine system can have profound effects on timing behavior. For instance, the administration of dopaminergic agonists, such as cocaine, causes behavior to occur earlier, as shown in a leftward shift of the timing functions, consistent with the speeding up of an internal clock (Matell et al., 2004). Interestingly, at the

same dose, cocaine speeds up the timing of a 90-second interval three times more than when timing a 30-second interval, suggesting that the effect of the drug is proportional, or scalar, to the timed interval (suggesting that the clock speed mediates the effect). Conversely, the administration of dopaminergic antagonists, such as haloperidol, produces a rightward shift of the timing functions, consistent with the slowing down of an internal clock (Macdonald & Meck, 2005; Meck, 1996). Such findings have been interpreted within the framework of the dopamine clock hypothesis (Meck, 1998), which states that the speed of the internal clock depends on dopaminergic (DAergic) activity (i.e., increased dopamine release speeds up a subject's internal clock).

A theory that further explains this phenomenon and attributes a critical role to dopamine in interval timing is the striatal beat frequency model (SBF) (Matell & Meck, 2004). According to this model, it is proposed that striatal spiny neurons integrate the activity of large networks of cortical oscillators located in the prefrontal cortex (PFC). These cortical oscillators exhibit diverse frequency responses and are influenced by the mesocortical dopamine pathway. The effect of mesocortical dopamine on clock speed is thought to be mediated through its modulation of the frequency of neural oscillations in the prefrontal cortex. Mesocortical dopamine is thought to modulate the activity and synchronization of these oscillatory networks, thereby influencing the speed at which the internal clock operates (Oprisan & Balci, 2013).

The SBF model suggests that the oscillatory properties of neurons play a critical role in timing behavior, and the frequency or beat of these neural oscillations represents the timing of events or durations. When timing an interval, the cortical oscillators initially become phase-locked with the dopaminergic input from the ventral tegmental area (VTA) to the

prefrontal cortex. However, due to their distinct frequencies, the oscillators quickly fall out of phase with each other. At the time of reinforcement or feedback, the series of oscillators is read out, and medium spiny neurons determine whether they are spiking or not. The learning of time intervals is presumed to involve dopamine-dependent neural plasticity in the nigrostriatal dopamine pathway.

Overall, both the dopamine clock hypothesis and the SBF model provide insights into the influence of dopamine on clock speed and the integration of neural oscillations in the timing processes. These theoretical frameworks contribute to our understanding of the neural mechanisms underlying interval timing and highlight the importance of dopaminergic activity in modulating timing behavior.

1.2.3: Impaired interval timing

An impaired ability to process time in the seconds-to-minutes range is found in patients with disorders that involve dysfunctioning dopaminergic pathways, such as Parkinson's disease (e.g., Malapani et al., 1998, 2002), Attention Deficit Hyperactivity Disorder (ADHD) (e.g., Barkley, 1997; Smith et al., 2002; Coull et al., 2011; Wilson et al., 2013; Walg et al., 2015), and schizophrenia (e.g., Rammsayer, 1990; Tracy et al., 1998; Volz et al., 2001; Elvevåg et al., 2004; Penney et al., 2005).

In Parkinson’s disease, the degeneration of dopaminergic neurons in the substantia nigra (SN) disrupts the normal functioning of the basal ganglia, leading to impairments in timing and temporal processing. Patients with Parkinson's disease often exhibit difficulties in perceiving and reproducing time intervals accurately. The SBF model (Matell & Meck, 2004) provides a

more detailed explanation of timing deficits in Parkinson's disease. This model emphasizes the role of neural oscillations and synchronization in timing processes. In Parkinson's disease, the degeneration of dopaminergic neurons disrupts the modulation of neural oscillations in the basal ganglia and prefrontal cortex. As a result, the synchronization of cortical oscillators, which are crucial for accurate timing, is impaired. This desynchronization leads to timing disturbances and difficulties in distinguishing between different durations. Moreover, patients with Parkinson's disease are unable to time two or more durations independently. The reproduced duration for the two criterion durations tend to migrate towards each other (Malapani et al., 1998, 2002).

Individuals with ADHD also often exhibit deficits in interval timing. This is thought to likely emerge from structural abnormalities in medial/superior frontal and basal ganglia structures (Brieber et al., 2007; Bos et al., 2017; Hoogman et al., 2017) as well as from dysfunctions in the dopaminergic system (Nieoullon, 2002). Theoretical frameworks, such as the SBF model (Matell & Meck, 2004), propose that attention and arousal can influence the speed of timing processes. This occurs through the activation or deactivation of a switch that governs the counting of pulses generated by an "oscillating clock" (Egeland et al., 2012). In the context of ADHD, it is suggested that individuals have an accelerated internal clock, causing time intervals to subjectively appear longer than their actual duration. One hypothesis is that individuals with ADHD may exhibit reduced coherence and synchronization among cortical oscillators, leading to less accurate timing. The impaired regulation of dopamine levels in the mesocortical pathway may contribute to this dysregulation of cortical oscillations. Specifically, abnormalities in the dopaminergic modulation of the prefrontal cortex, where the oscillators

are located, can disrupt the precise coordination required for accurate interval timing. Moreover, the SBF model proposes that the readout of timing information occurs through medium spiny neurons in the striatum. Dysfunction in the dopaminergic projections to the striatum (nigrastriatal), as seen in ADHD, can further impact the processing and integration of timing-related signals. This disruption may result in deficits in the encoding and decoding of temporal information, leading to timing impairments in individuals with ADHD.

In the case of schizophrenia, abnormalities in dopaminergic neurotransmission have been implicated in the disturbances of interval timing processes. Patients with schizophrenia commonly show deficits in perceiving time intervals and exhibit altered time perception, characterized by temporal distortions and difficulties in estimating the duration of events (Rammsayer, 1990; Tracy et al., 1998; Volz et al., 2001; Elvevåg et al., 2004; Penney et al., 2005). The dopaminergic abnormalities in schizophrenia can disrupt the precise coordination of neural oscillations involved in interval timing, as proposed by the SBF model. Specifically, irregularities in dopamine signaling, particularly in the mesocortical pathway, may impact the modulation of cortical oscillators, leading to timing impairments. These temporal processing impairments in schizophrenia may contribute to cognitive dysfunction and disorganized thought processes observed in the disorder.

1.2.4: Studying interval timing in non-human animals

Various behavioral methods have been developed to demonstrate and investigate interval timing in non-human animals. From these, one of the most commonly used procedures is the Peak Interval (PI) procedure (Catania, 1970; Roberts, 1981), which comprises two trial

types: Fixed Interval (FI) and Peak Interval (PI). In FI trials, a reward is made available after a fixed delay following a point event or stimulus (e.g., turning on the light, onset of an auditory stimulus). To receive the reward, the animal must perform a response or action that is reinforced only if it is emitted after the fixed interval. In contrast, the trial duration in PI trials is significantly extended (e.g., 3xFI) but no reward is provided. Consequently, animals can only rely on passage of time to realize the omission of the normally expected reward. The response rate as a function of time in PI trials is typically used to estimate the change in the expectancy of reward as a function of time. For instance, when the animal's response rate is averaged over many PI trials the response curve resembles a bell-curve (see Figure 2), with the location of its peak reflecting the trial time at which the animal's reward expectancy is highest. The proximity of the peak time to the actual delay to reward availability (i.e., FI schedule) is treated as a measure of timing accuracy. The width of the response curve reflects response variability, which is assumed to be a manifestation of the animal's uncertainty in its representation of the target interval and/or elapsed time (Freestone & Balci, 2009; Balci et al, 2013; Meck, 2003). This is referred to as timing uncertainty.

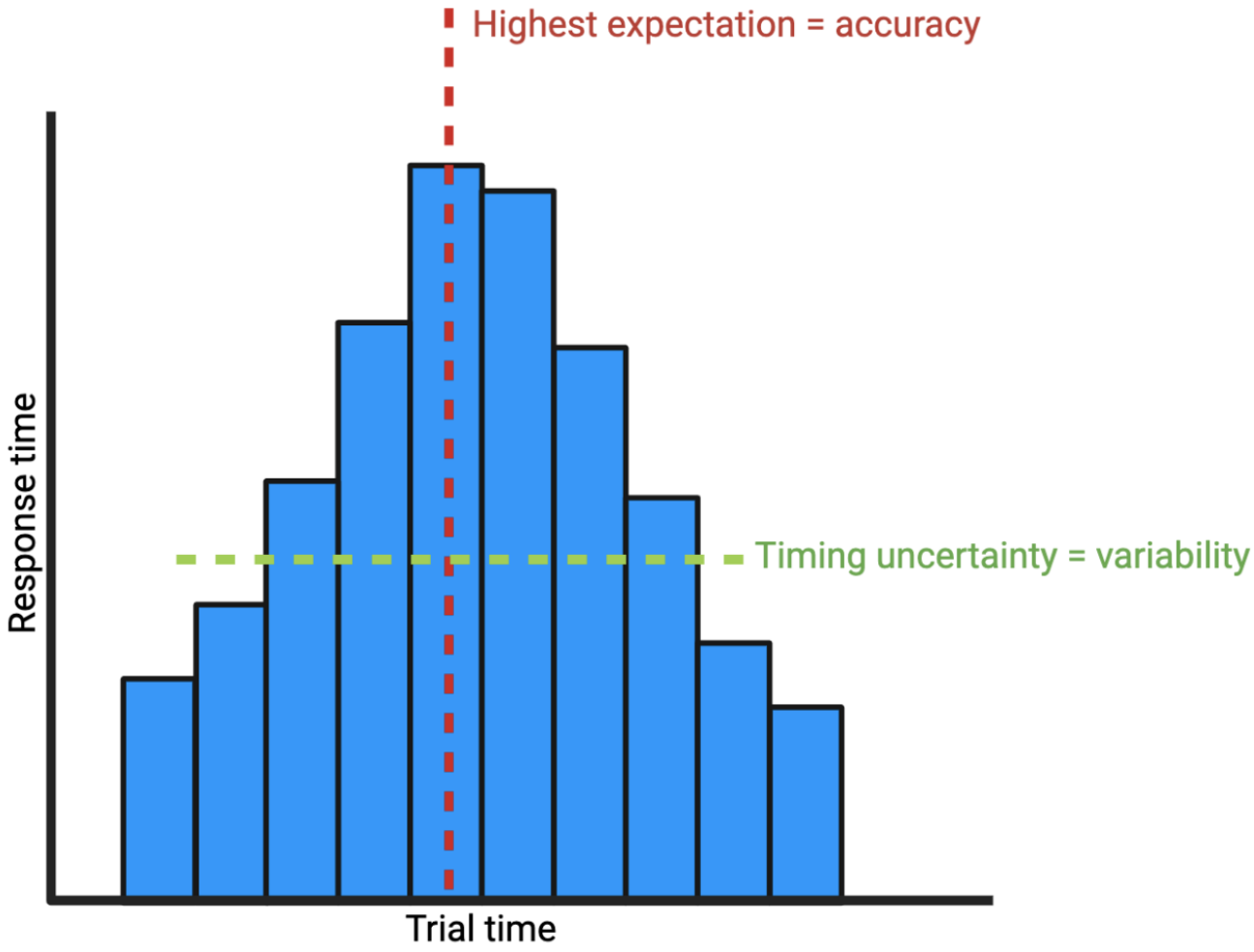


Figure 2: Response rate as a function of trial time calculated as the average number of responses emitted each time bin during peak interval (PI) trials. The peak location of the resultant bell curve is used as a proxy for the trial time at which the animal has highest reward expectancy (aka timing accuracy). The width of the same response curve is used as a proxy for response variability as the manifestation of the animal's uncertainty. (Designed on biorender.com)

Another method commonly employed in interval timing research is the Differential Reinforcement of Low Rates of Responding (DRL) task (Ferster, 1970). The DRL task is designed to shape and maintain low rates of responding within a specific time frame by having to withhold their response for a certain duration before initiating a subsequent response. The mean inter-response time in the DRL task typically adapts to the minimum wait time requirement reflecting the temporal control over waiting behavior.

These tasks have significantly broadened the scope of interval timing research. Although, all tasks mentioned have a shared characteristic among them, which is the substantial training duration needed for both humans and non-human animals to attain consistent performance in the tasks. However, the Differential Reinforcement of Response Duration (DRRD) (Skinner, 1938) protocol may allow for faster training.

The DRRD task investigates the duration of the organism's own response as the temporal interval of interest, such as how long the lever was pressed, or how long a nose-poke response was sustained (Lejeune & Jasselette, 1987; Reyes et al., 2020). This task involves the reinforcement of specific response durations rather than response rates. In these tasks, subjects are trained to emit responses that fall within a particular duration window to receive reinforcement. The duration window can be defined by upper and lower limits, and responses that fall outside this window are not reinforced.

In their 2020 study, Reyes et al. employed the DRRDD task, aiming to develop an innovative approach to achieve comparable performance without the prolonged training required by previous tasks. The authors compared three different training protocols. The first protocol, group "Time-Out" involved training rats using the DRRD task. In this setup, rats were

required to sustain a lever-press response for progressively increasing durations. Notably, instances of incorrect responses were met with a timeout period during which reinforcement was withheld. The second protocol, group "No-Time-Out", closely paralleled the Time-Out group's training regimen. However, there was an absence of timeout periods following incorrect responses. In this scenario, all lever-press responses, regardless of their duration, were deemed valid and held the potential for receiving reinforcement. Lastly, the third protocol, "Fixed" group , entailed training rats with an unchanging criterion time of 1.2 seconds throughout all training sessions. Notably, this group was characterized by the absence of timeout periods altogether. Rats within this group were required to sustain their lever-press response for a minimum duration of 1.2 seconds to receive reinforcement. Remarkably, the results of the study revealed a significant impact of eliminating timeout periods following incorrect responses. This alteration substantially expedited the learning process, to the extent that the performance of rats in the No-Time-Out group at the conclusion of their first session closely approximated the performance achieved by rats subjected to numerous sessions of training in other protocols.

With this protocol, Reyes et al., (2020) identified a procedure that enabled rats to achieve performance levels similar to those obtained with long-term training after just a single session of 30 trials. This finding is particularly significant as it reduces the time and effort required to establish stable behavioral performance in the DRRD task. By streamlining the training process, researchers can more efficiently investigate temporal learning and its underlying mechanisms. One interesting observation made by Reyes et al. was that the distribution of responses in the rats was initially unimodal, meaning that most responses occurred around the target time of 1.2 seconds. However, as the rats underwent training and

improved their performance, a second peak in response distribution emerged and gradually shifted towards longer time intervals. This observation suggests that the rats' time perception and ability to discriminate different durations were refined as they became more proficient in the task.

The DRRD tasks offer the advantage of faster training; however, their efficiency and reliability compared to other tasks, such as DRL, need to be further examined. A comparative study by Jasselette et al., (1990), researchers investigated pigeons' performance in the DRL and DRRD tasks, revealing both similarities and differences between the tasks. Performance during both tasks showed adherence to the generalized Weber's Law, which states that the ability to perceive a constant change in a quantity decreases in proportion to its magnitude. However, certain distinctions were also observed. Particularly noteworthy was the prominence of a positive bias in responding, particularly manifested in a behavior termed the "perching response," within the context of the DRRD task when juxtaposed with the DRL schedule. The perching response refers to a behavior where the subjects, in this case, pigeons, exhibit a propensity to position themselves on the lever, possibly reflecting an anticipation of the impending trial.A difference is that the DRRD tasks typically incorporate an intertrial interval (ITI), which is a period of time between the completion of one trial or stimulus presentation and the start of the subsequent trial, whereas DRL tasks do not present an ITI.

1.2.5: Scalar timing

Irrespective of the tasks used, the psychophysical analysis of timing responses suggest a specific relationship between the target time and the variability of timing responses (e.g. Buhusi

& Oprisan, 2013; Gibbon, 1977; Gibbon et al., 1984). One of these core features is that the variability in estimating a duration is proportional to the duration to be timed, a property known as scalar timing. In statistical terms, scalar timing refers to the proportionality between the standard deviation and mean of the timed responses and thus the constancy of the coefficient of variation for different target intervals and individual performance. Scalar property of interval timing is one way to explain Weber's law. Weber's law predicts that the ratio of the difference threshold (Δ I) to the initial stimulus intensity (I) is constant (k) (see Equation 1) (Gallistel & Gibbon, 2000):

$$\Delta I/I = k \tag{1}$$

Weber's law can also be observed in our daily experiences. For example, imagine your friend tells you that they will arrive in the coffee shop within a minute but they arrive after three minutes; you are likely to notice the delay and maybe act on it by texting your friend. However, if your friend arrives after an hour and four minutes, the additional four minute delay may go unnoticed. This illustrates how our sensitivity to time changes can be influenced by the duration being timed. The scalar property shows that the very same principle applies to our perception of time in seconds-to-minutes range by showing that endogenous timing uncertainty is proportional to the represented time interval.

1.3: Timing uncertainty

Scalar variability in timed responses is assumed to result from scalar representational uncertainty about time intervals, which is explained by different underlying generative processes assumed by computational models of interval timing. For instance, the information processing variant of Scalar Expectancy Theory (SET) (Gibbon, 1977, 1992; Gibbon et al., 1984) states that interval timing is manifested via information processing at three distinct phases; a clock, a memory, and a decision phase (see Figure 3). SET assumes that hypothetical pulses are emitted regularly by a Poisson pacemaker and integrated by, and temporarily stored in, an accumulator (working memory component). At the time of reinforcement, the number of pulses stored in the accumulator is transferred to reference memory (long-term memory) during which it is multiplied by a normally distributed random variable with a mean of 1 (Gibbon et al., 1984; Gibbon & Church, 1990; Balci & Simen, 2016). This is assumed to be the source of scalar noise and uncertainty in time representations (see Figure 2). Timed responses depend on the ratio-based comparison between the value stored in the reference memory and the current accumulator total and this value is assumed to be computed at the decision stage.

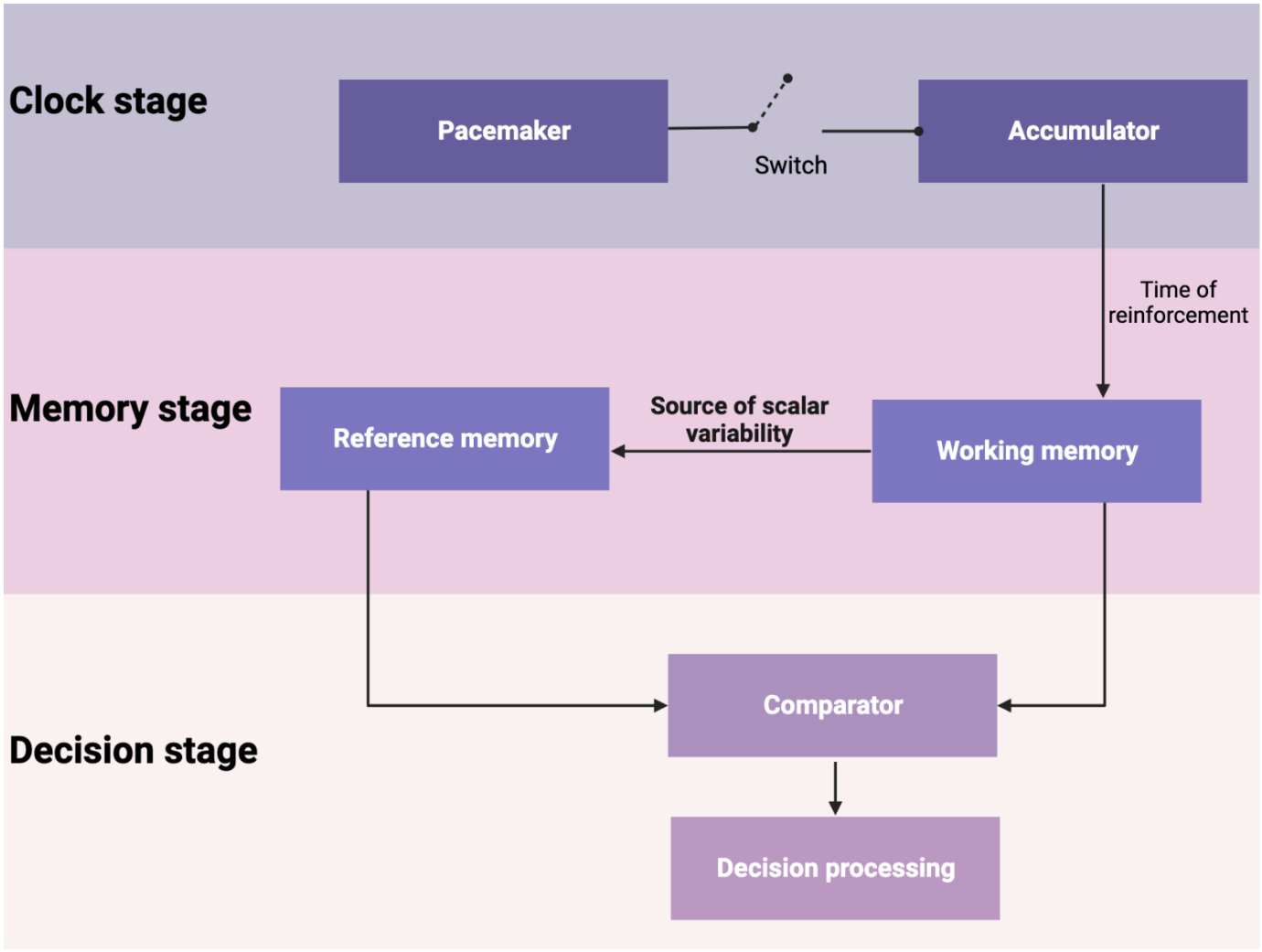


Figure 3: Information processing variant of the Scalar Expectancy Theory (SET) model. Figure adapted from Church (1984), Gibbon et al., (1984), and Meck (1984). (Designed on biorender.com)

Consistent with this view, Creelman's pacemaker accumulator model (CPAM) (Creelman, 1963) assumes that the accumulation of pulses is stored in memory and subject to noise as there is variability in the storage and retrieval of timing criterion to and from memory. Other models attribute timing uncertainty to the accumulation of clock signals. For instance, Treisman's pacemaker accumulator model (TPAM) (Treisman, 1963) assumes variability in the rate at which the clock signals are emitted between trials. More recently, Simen et al. (2011) and Balci and Simen (2016) attributed the timing uncertainty to the noise that results from the integration between Poisson excitatory and inhibitory inputs.

Despite the wide-spread study of timing uncertainty based on mathematical models, its neural basis has not been well studied. To date, one recent study by Çavdaroğlu and colleagues (2021) discovered that the CA3 subregion of the ventral hippocampus (vCA3) is critical in regulating timing uncertainty. In this study, rats were trained in a variant of the DRL task and found that post-training chemogenetic inhibition of the vCA3 reduced timing uncertainty without affecting mean wait times.

1.3.1: Adjusting behaviour optimally

Crucially, no matter the source of timing uncertainty, the level of uncertainty seems to be integrated into decisions in a normative fashion. For instance, when subjects are required to wait for a minimum amount of time before receiving a scheduled reward, optimal wait times are observed. Importantly, these optimal wait times have a non-linear relation (negatively accelerating) with the level of timing uncertainty. In other words, organisms adjust their behavior near-optimally by prolonging their waiting times considering the degree of the level of

uncertainty in their time estimates. For example, imagine you have an important meeting to attend, and you need to estimate how much time it will take you to reach your destination. If you know that your usual commute time has high variability due to unpredictable traffic conditions, you are likely to factor in additional time to account for potential delays. This adjustment demonstrates an intuitive application of timing uncertainty, as you adapt your travel plans by allocating a longer duration to ensure you arrive on time, considering the unpredictable nature of traffic.

The ability of animals to consider their inherent timing uncertainty and adjust their behavior implies that individuals with more accurate timing abilities would likely exhibit greater confidence in their choices and responses related to time. Foote and Crystal (2007) conducted an experiment with rats that indirectly supports that prediction. In their study, rats were trained to categorize durations as either shorter or longer than 4 seconds (i.e., a variant of the temporal bisection task). Correct categorizations were reinforced. Due to the presence of endogenous timing uncertainty, durations close to the 4 seconds were more difficult to discern as short or long. To investigate whether rats considered their temporal precision, Foote and Crystal (2007) introduced a modified task with an additional sure but smaller reward option. Choosing this option always resulted in a reward, regardless of the duration, but the reward magnitude was smaller. This allowed the researchers to examine whether rats took into account their timing uncertainty. If a rat was less certain about its temporal judgment, it would be more likely to choose the small but guaranteed reward. Although rats consistently chose either short or long for extreme durations (e.g., 2 and 8 seconds), rats frequently opted for the small but sure reward for durations that were more ambiguous (close to the bisection point). This finding

suggests that rats may have considered their inherent temporal uncertainty when making decisions, weighing their timing judgments and adjusting their choices accordingly. However, it is important to note that an alternative explanation exists, as it is possible that the rats in this experiment learned the differential reinforcement of different time intervals rather than explicitly accounting for their timing uncertainty (Jozefowiez et al., 2010).

Gür et al., (2022) investigated a similar question, whether animals optimize their timing behaviour, using a two-second DRRD task. This task required mice to sustain a lever press for a minimum amount of time to receive reinforcement. When the lever was released before the minimum required duration, the lever was retracted, and the trial ended without reward delivery. Results showed mean response durations were positively biased, meaning they were longer than the minimum requirement, and the extent of bias was predicted by the level of endogenous timing uncertainty. Researchers discovered a strikingly clever approach in mice, where they nearly maximized the rate at which they earned rewards in this task. By prolonging their lever-press durations just a bit longer than the required minimum, the mice seemed to tactically exploit timing nuances. This behavior allowed them to make the most of the task, achieving a higher frequency of successful reward outcomes. This finding underscores the mice's ability to dynamically adjust their timing behavior, highlighting their ability to make timing-based decisions that optimize their reward collection.

Kononowicz et al., (2022) also recently employed a DRRD task to test temporal behaviour optimization. The task required rats to press or demarcate a minimum requirement of 3.2 seconds with a lever. Consistent with other findings (Gür et al., 2022), the rats displayed a positive bias in their mean response durations.

These studies suggest that organisms may be able to keep track of the direction and magnitude of their timing errors (Akdoğan & Balcı, 2017), which I investigated in mice. It is unknown how, regardless of their timing uncertainty, both human and non-human animals can adjust their behaviour near optimally.

1.4: Error monitoring

One of the possibilities as to how both human and non-human animals can adjust their behaviour near-optimally (e.g., Gür et al., 2022) is that they can keep track of their timing uncertainty and plan their decisions accordingly. If so, since variability would result in timing error, one way for animals to estimate the level of variability is based on the level of their manifested timing errors. This raises the possibility that one knows whether and how much they have under- or over-estimated the duration of an event in a trial without any feedback, which we call metric error monitoring (MEM) (Yallak & Balcı, 2021).

1.4.1: Investigating MEM in mice

It is this question that drives my research objective —investigating the presence and mechanisms of metric error monitoring in mice, in the context of interval timing.

1.4.2: MEM and enhanced reward expectations

MEM can be considered as an element linked to the heightened expectation for rewards (Akdoğan & Balcı, 2017). This encompasses maintaining awareness of mental states and cognitive functions, and possessing the capacity to introspectively assess and appraise one's own performance. . While established within the human context, ongoing research endeavors direct attention towards understanding the extent to which non-human species exhibit this concept. This investigative pursuit provides insights into shared cognitive capacities across species and uncovers the underlying cognitive mechanisms guiding decision-making,

problem-solving, and self-regulation.This research contributes to a more comprehensive understanding of the evolutionary origins and cognitive capabilities of different species, challenging previous assumptions about the uniqueness of these abilities in humans.

1.4.2: Previous two-alternative forced-choice (2AFC) studies

Traditionally, error monitoring has been studied in humans using two-alternative forced-choice (2AFC) paradigms (e.g., Chua, Schacter, & Sperling, 2009; Fleming, Dolan, & Frith, 2012; Samaha & Postle, 2017; Siedlecka, Paulewicz, & Wierzchoń, 2016; Wierzchoń, Paulewicz, Asanowicz, Timmermans, & Cleeremans, 2014; Zehetleitner & Rausch, 2013). In these paradigms, individuals are presented with two options or stimuli and are required to make a choice or response based on a specific criterion or task rule. For instance, participants in a 2AFC study may be presented with two different images, A and B, and they are instructed to indicate whether A or B is brighter. Each trial presents a different pair of images, and participants must make their choice by pressing a corresponding button or key for image A or image B.

It has been shown that various species including humans, primates (e.g., Freedman et a., 2011), and rats (Zènon et al., 2008; Kepecs et al., 2008) can keep track of their binary errors in their choice behavior using various methods. Freedman et al., (2011) compared the categorization behavior of humans and nonhuman primates using 2AFC tasks. Participants (humans) and monkeys were presented with visual stimuli and had to categorize them into two different groups. The study examined the cognitive strategies and neural correlates involved in categorization and showed both species could keep track of their binary errors. Similarly, in rats, sensory decision-making was investigated using a 2AFC task by Zènon et al., (2008). Rats were

presented with auditory stimuli of different intensities and had to make a choice based on the stimulus intensity.

A main limitation of these studies is that trial-based errors in 2AFC tasks are binary in nature, while many errors encountered in real-life scenarios have directionality and vary in magnitude. For example, you are a professional tennis player and you are playing a match. During the game, you are constantly making perceptual decisions about the trajectory, speed, angle of your racket, and spin of the ball to determine how to respond and hit the ball back. In this context, errors are not simply binary outcomes (e.g., hitting the ball in or out), but they also involve directionality and vary in magnitude. This limitation underscores the significance of investigating the metric components of error monitoring. To illustrate this, consider the same task involving images A and B where participants are required to determine which image is brighter. Following their response, the experimenter could inquire about the extent to which participants perceived image A as brighter than image B, as well as their level of confidence in their response, and whether they believed they had underestimated or overestimated the level of brightness. Incorporating these additional parameters allows for a more comprehensive measurement of the metric aspects of error monitoring, providing insights into the precise characterization of errors.

1.4.3: MEM in humans

In recent studies employing similar tasks to that mentioned above (e.g., Akdoğan & Balcı, 2017; Duyan & Balcı, 2018, 2019; Doenyas, et al., 2019; Kononowicz, Roger, & van Wassenhove, 2019; Kononowicz & van Wassenhove, 2019; Yallak & Balci, 2022), it has been

shown that humans possess the ability to monitor both the direction and magnitude of errors when reproducing target time intervals.

In Akdoğan and Balcı's study (2017), participants were asked to reproduce target durations ranging from 1.5 seconds to 6 seconds as accurately as possible. After each reproduction, participants were asked to retrospectively rate their confidence in their temporal estimates on a numerical scale between 1 (low confidence) and 3 (high confidence) and to judge if their response time was earlier (shorter) or later (longer) than the target interval. They were instructed to respond as fast as possible both for confidence ratings and directionality judgments. No performance feedback was provided to the participants. Results of this study showed for the first time that humans can correctly keep track of the direction and magnitude of their errors in the reproduction of target time intervals. There were a handful of other studies that showcased metric error monitoring soon after Akdoğan and Balcı's study (2017).

Following, Duyan and Balcı, (2018) showed that human participants can keep track of the direction and magnitude of metric errors in not only temporal domains but also in their estimates of numerosities. They achieved this by showing participants a random dot array for a brief amount of time, following, participants were asked to record how many dots they believed there were, along with their confidence rating, how close they believed their estimate was in relation to the actual amount, and whether they thought they over- or under-shot the target. Duyan and Balcı (2018) showcased that participants not only accurately gauged the number of dots presented (magnitude) but also astutely discerned whether they had surpassed or fallen short of the mark (direction), showing MEM abilities in numerosity in humans.

Kononowicz et al. (2019) also reported on metric error monitoring and "temporal metacognition" abilities in humans using newly designed tasks and neuroimaging. Metacognition, as defined by Flavell, (1979) refers to the cognitive process involved in monitoring and regulating one's own learning and thinking. It involves having awareness and control about one's own mental state and cognitive processes, and the ability to reflect on and evaluate performance. Participants in this study were asked to produce time intervals of 1.45 seconds and to subsequently rate their produced interval on a continuous scale going from "too short" to "too long". In this temporal production task, participants self-initiated the time interval by button press and terminated it with a second button press when they considered the target duration had elapsed. Participants's brain activity was captured with combined magneto- and electro-encephalography (MEG-EEG) while performing the task. Kononowicz et al., (2019) proposed that when evaluating their ability to judge the timing of their actions, participants depended on an internal variable that represented the duration of their intended goal. It is hypothesized that this internal variable serves dual roles, both in estimating the timing of actions (first-order judgment - FOJ) and in evaluating their own judgments (second-order judgment - SOJ) (Fleming et al., 2012). Researchers believe internal dynamics in timing are mediated by oscillatory or state-dependent network dynamics (Buhusi & Meck, 2005; Laje and Buonomano, 2013; Allman et al., 2014; Gu et al., 2015; van Wassenhove, 2016; Bueno et al., 2017). Time duration may be coded by the power of beta (β) oscillations, which refer to the rhythmic neural activity in the brain that occurs within a specific frequency range of 15 to 40 Hz. Kononowicz et al., (2019) reported participants reliably estimated the direction and magnitude of their timing errors. They also provided additional evidence for β oscillations representing an

internal variable that determines the temporal duration using MEG. They found that the patterns of β oscillations in the human brain can predict both the ability to estimate time intervals and the accuracy of our judgments about them. These findings suggest that the level of network inhibition represented by β power acts as a variable that determines the direction of the network's activity, serving as a natural code for perceiving duration.

Additionally, Riemer et al. (2019) investigated the degree to which humans depend on external feedback to adjust their timing behavior and make accuracy judgments. Researchers asked participants to repeatedly reproduce a temporal interval of three seconds and provided them with different types of feedback on their performance. Feedback provided information either about the magnitude and the direction of errors (signed feedback), or about the error magnitude alone (absolute feedback). Signed feedback resulted in more behavioral adjustments that were opposite to the direction of the error in subsequent trials, as well as reduced bias in temporal estimates, and participants produced a more accurate and better calibrated performance when compared with the absolute feedback group. This study illustrated that directional information was not intrinsically accessible to the subject and that the participant's internal timing error representation failed to include that error direction. Furthermore, subjects assigned to the absolute feedback group also tended to report an over-reproduction of the interval duration when in reality, they were under-reproducing.

To further understand this, the impact of non-directional feedback and reinforcement learning on time perception were examined by Bader and Wiener (2021) in a unique temporal reproduction paradigm that involved a mixed set of interval durations and the opportunity to repeat every trial immediately after receiving feedback, essentially allowing a correction or

"redo." Two groups of participants were presented with different versions of the task. In one group, non-directional feedback was given after each response, whereas the other group received no feedback at all. Both groups showed improvements in their temporal estimates during the "redo" trials. This suggests that participants possess an inherent capability to adjust their temporal responses, even in the absence of directional information or any feedback. The group that received feedback also demonstrated increased precision in their temporal estimates during the "redo" trials, indicating that feedback may have a specific role in reducing noise and improving the accuracy of temporal judgments.

More recently, Yallak and Balci (2021) investigated individuals in their accuracy in temporal, spatial, and numeric domains. In the temporal task, participants were asked to reproduce target durations of 1.5 seconds, 3 seconds, and 4.5 seconds directly after the target duration was presented to them. Following, participants rated their confidence on a 3-point scale, 1 (low confidence), 2 (medium confidence), and 3 (high confidence) and indicated the direction of the error in their reproduction (shorter or longer). The spatial reproduction task required participants to reproduce target line lengths that were presented in that trial. Following, participants were again asked to rate their confidence and direction of the error in their reproduction. The numerical estimation task was very similar to that of Duyan and Balcı (2018), in which participants were shown an image with a number of dots, and asked to estimate how many there were, as well as their confidence and direction. Their results suggest that error monitoring ability operates similarly or relies on a common factor across different metric domains (temporal, spatial, and numeric).

All of these studies investigated MEM by requiring participants to make judgments regarding their errors. Unintentionally, this may have activated or influenced the potential association between the primary timing task and the secondary judgments. Therefore, Yallak and Balci (2022) developed a study that indirectly tested MEM. Participants were tasked with reproducing a target interval (first-order judgment - FOJ), and each reproduction was assigned a score that exponentially decreased in value based on its deviation from the target interval. Rather than directly assessing their second-order judgments (SOJ), participants were given the choice to opt-out of a trial after their FOJ if they preferred the score in that trial, that they have not seen yet, to not to be included in the average score to be maximized. In a second experiment, the decline option was only available in some trials to ensure participants were performing as accurately as possible in all trials. Results showed that participants declined the reproductions that were distant from the target duration more frequently than the reproductions that were closer to the target duration. Thus, participants were able to successfully identify trials in which they had a large enough timing error and adaptively declined these trials.

Collectively, these studies highlight the robust presence of metric error monitoring abilities in humans across different contexts. The ability to monitor and evaluate errors in various metric domains enables us to adjust our behavior, improve future decisions, and optimize performance. Further research in this area will deepen our understanding of the underlying mechanisms and implications of metric error monitoring, enhancing our knowledge of human cognitive processes.

1.4.4: Impaired MEM

The MEM process is known to be disrupted in certain neurological disorders. Specifically, individuals with autism spectrum disorder (ASD) frequently experience challenges in error monitoring, leading to difficulties in accurately identifying and appropriately addressing their own errors (Doenyas et al.,2018). These impairments manifest as difficulties in social interactions as the cognitive domains that support these interactions include perceptual decision-making, timing, and error monitoring (Doenyas et al., 2018).

A previous study by Brosnan et al. (2016) tested math performance monitoring, asking if participants thought they got the answer to a math problem right or wrong, and found that individuals with ASD were more likely than typically developing (TD) participants to think that they got an incorrect answer correct. Doenyas et al., (2018) then tested the MEM abilities in ASD children by employing the temporal reproduction task used in Akdoğan and Balcı, (2017) and asked participants to judge the direction and magnitude of errors in their temporal reproductions. This task for the first time investigated the temporal metric error monitoring ability of children with ASD and children in general. Doenyas et al., (2018) findings indicate that children with ASD exhibit a specific impairment in performance monitoring. Unlike TD children, the confidence ratings of children with ASD did not align with their actual performance in either the perceptual decision-making task or the interval timing task. This confirms the discrepancy in error monitoring in ASD children.

Similarly, in obsessive-compulsive disorder (OCD), error monitoring processes are also disrupted, although in a different manner. It has been proposed that cortico-striatal hyperactivity leads to a persistently high error signal, ultimately resulting in the

psychopathology characteristics of OCD (Grundler et al., 2009; Remijnse et al., 2006). Individuals with OCD often experience intrusive, unwanted thoughts (obsessions) and engage in repetitive, ritualistic behaviors (compulsions) to alleviate anxiety or distress (Grützmann, 2016; Carrasco et al., 2013). The brain's error monitoring system compares intended responses (or "expected outcomes") to actual responses (or "actual outcomes" in environmental stimuli, thoughts, feelings, and actions), and generates an error signal when a conflict in these outcomes is detected. It has been suggested that this error signal is amplified in individuals with OCD, leading to the feeling that something is not right, which causes irrational fears or obsessions. Additionally, if an action was not completed correctly according to a set of internal unattainable rules, this triggers repetitive, compensatory behaviors. The compulsive behaviors are often triggered by perceived errors or the need to prevent potential errors from occurring.

Understanding the impairments in error monitoring processes as seen in ASD and OCD can contribute to a better understanding of the cognitive and neural mechanisms underlying OCD and may inform the development of targeted interventions and treatment approaches.

1.4.5: MEM in rats

Studies have investigated metacognition-like behaviour in rats in non-magnitude domains. In a study by Kirk et al., (2014) rats were trained to press a lever to get a reward. This lever press also signaled the presence of another reward in a specific arm of a T-maze. Even when the immediate reward was removed later on, the rats continued to press the lever to find out where the food was in the maze. The rats became even more interested in seeking information when the lever press provided more bits of information, such as testing them in a

maze with eight arms instead of two. However, when the food location became certain or predictable, the rats did not continue to press the lever seeking information.

Following, Kheifets et al., (2017) showed that rats and mice can distinguish between their own measurement error and exogenous timing uncertainty. The researchers designed tasks that involved timing intervals and introduced conditions where the animals had to differentiate between their own internal timing mechanisms and external factors that could potentially disrupt their timing accuracy. When faced with increased measurement error or external timing variability, the animals exhibited distinct patterns of response, indicating their awareness and sensitivity to different sources of temporal uncertainty and providing compelling evidence that both rats and mice were capable of distinguishing between their own measurement errors and exogenous timing uncertainty. This ability can be explained by the presence of multiple independent clocks in the subjects' timing mechanisms which is supported by multiple studies (e.g., Vickers, 1979; Meck & Church, 1984; Narayanan & Laubac, 2008, Akdoğan & Balcı, 2017).

Templer et al., (2017) explored rats' ability to assess their own memory strength. To achieve this, the researchers introduced a decline option within a memory task where rats were presented with a series of four-choice odor-based tests known as delayed match-to-sample (DMTS). The decline option allowed rats to opt-out of specific memory tests. The results of the study revealed that rats performed significantly better on tests they actively chose to take, as opposed to tests they were compelled to take. This suggests that the rats were able to distinguish between remembering and forgetting. The researchers addressed the alternative explanation that the rats' use of the decline option was based on external test-specific cues that

became associated with increased rewards over time. To explore this possibility, three generalization tests were conducted where external conditions were inconsistent and could not serve as discriminative cues. Remarkably, the rats demonstrated an adaptive transfer of the decline response in these tests. They used the decline option effectively when no sample was presented, when multiple samples were provided to enhance memory, and when memory strength was modulated by varying the retention interval. An important finding from the study was that rats made choices to take or decline the test before encountering the memory test itself, suggesting that their responding was based on internal cues rather than external ones.

A study by Joo et al., (2021) explored the relationship between memory retrieval, memory confidence, and memory-guided decisions. It aimed to shed light on how confidence in memories is utilized in the decision-making process. To investigate this, the researchers designed a spatial memory task where rats were engaged in a decision-making task that relied on their memory of locations. The rats were required to make temporal bets, indicating their confidence in the accuracy of their memory. The bets influenced the potential rewards, with larger rewards associated with correct choices. The study observed that rats exhibited a higher tendency to bet more for correct choices compared to incorrect choices, revealing that rat behavior reflected memory confidence.

A recent and novel study by Kononowicz and colleagues (Kononowicz et al., 2022) provided a compelling example of the complexity of the error representations in non-human animals by showing self-monitoring of temporal errors in rats for the first time. These findings have great significance, as previous studies only show that humans have MEM abilities (e.g., Akdoğan & Balcı, 2017; Duyan & Balcı, 2018, 2019; Doenyas, et al., 2019; Kononowicz, Roger, &

van Wassenhove, 2019; Kononowicz & van Wassenhove, 2019; Yallak & Balci, 2022). Kononowicz et al.'s study (2022) involved training two groups of rats; one group demarcating the target minimum duration by pressing a lever twice, and the other group pressing and holding one lever for the target minimum duration. In line with previous work also using DRRD tasks (Gür et al., 2022), rats produced time intervals optimally with mean time productions longer than the minimum requirement. Temporal productions were categorized as those longer but close to the minimum duration (small errors), and much longer than the minimum duration (large errors). Following the time production, responding at a given port delivered 1 pellet after a large error and no pellets after a small error, whereas responding at the other port delivered 2 pellets after a small error but no pellets after a large error. The authors found that all rats tested in this task exhibited better than chance level performance by choosing the correct port defined for the magnitude of their timing error in that trial. The proportion of correct choices is a direct measure of temporal error monitoring, as the reward was conditional to the magnitude of error. Following, Kononowicz et al., (2022) discovered that rats use both their temporal error in the current trial as well as reward history when making decisions and choosing accurately. These findings prove that MEM is present in non-human animals and show an example of the complexity of the same error monitoring representations humans possess, in rats.

One limitation that should be considered when interpreting the findings of the study by Kononowicz et al. (2022) is the possibility that the observed performance of the rats may be attributed to the differential reinforcement of different responses rather than second-order responses guided by heightened cognitive awareness. In the study, the rats were trained to produce time intervals and received varying rewards based on the magnitude of their timing

error. The rats learned to associate specific responses with different levels of rewards, such as receiving one pellet for a large error and no pellets for a small error. This differential reinforcement schedule may have influenced the rats' behavior, leading them to make response choices based on the anticipation of rewards rather than solely relying on potential cognitive processes.

Furthermore, it is worth noting that Kononowicz et al., (2022) is not the only investigation of heightened cognitive abilities in non-human animals that has faced criticism regarding the potential influence of differential reinforcement rather than the heightened expectation for a reward. Foote and Crystal (2007) is another study that has been subjected to similar scrutiny. Foote and Crystal trained rats on a task involving temporal discrimination and provided different types of feedback based on their performance. Critiques of the study suggest that the observed behavior could be attributed to the animals learning to discriminate between the different feedback conditions rather than reflecting genuine cognitive monitoring. The concern raised in both the study by Kononowicz et al., (2022) and Foote and Crystal (2007) study is that the observed behavioral patterns may be the result of animals responding to specific cues or contingencies associated with differential reinforcement, rather than engaging in self evaluation or a heightened decision-making processes.

Another notable limitation in the investigation of MEM by Kononowicz et al., (2022) is the absence of error directionality judgments. Although their study successfully demonstrated self-monitoring of temporal errors in rats, it primarily focused on evaluating the magnitude of errors rather than considering the direction in which errors occurred. The rats' temporal productions were categorized solely as small errors or large errors, with different rewards

assigned based on error magnitude. Thus, the study did not explicitly account for the specific directionality of errors.

In addition to considering error directionality judgments, it would be beneficial to further investigate a decline option and incorporate well-controlled generalization tests in studies like the one conducted by Kononowicz et al., (2022). In Foote and Crystal's study (2007), rats had the option to decline the test during certain trials. Accurate performance on the duration test resulted in a large reward, whereas inaccurate performance resulted in no reward. Declining a test resulted in a small but guaranteed reward. Rats declined most frequently on difficult tests and showed lowest accuracy on difficult tests that could not be declined. The inclusion of a decline option provides an opportunity to examine whether nonhuman animals possess the ability to recognize and decline their own temporal productions when they perceive errors.

1.4.6: Error related negativity

The results of Kononowicz et al. (2022) study lay the foundation for novel research questions, such as how errors are coded in the brain. Previous human studies (Hajcak et al., 2006) have shown that there is an event related potential (ERP) component that signals binary errors. ERP refers to a specific electrical response recorded from the brain that is time-locked to a particular event or stimulus. When individuals perform tasks or engage in cognitive processes, their brain activity generates electrical potentials that can be measured using electroencephalography (EEG). Simply put, ERP is the brain activity that indexes the on-going monitoring of correct and incorrect behavior.

Error-related negativity (ERN) (Gehring et al., 2018) and positivity (Pe) are components of ERP waveforms recorded by EEG in human and non-human animals (see Figure 4). ERN is a response-locked negative deflection in ERPs that appears at about the same time as an incorrect behavioural response begins, and peaks between 70 and 120 ms after the behavioral output. The ERN is thought to reflect early error-processing activity of the anterior cingulate cortex (ACC), which is hypothesized to be the generator of the ERN and is a region of the brain involved in error detection, conflict monitoring, and cognitive control processes (Olvet and Hajack, 2008). Several functional imaging studies (e.g., Garavan et al., 2003) also found that the ACC of human participants engaged in reaction-time tasks was more activated on error trials than on correct trials.

More specifically, the ERN is thought to reflect the impact of phasic decreases in dopamine signals from the midbrain on areas of the ACC (Olvet & Hajack, 2008). When an individual makes an error, there is a rapid reduction in dopamine signals from the midbrain, leading to a temporary decrease in dopamine levels in the ACC. This phasic reduction in dopamine signals is believed to trigger the generation of the ERN in the brain's electrical activity, leading to the observed negative deflection in the ERP waveform (Holroyd & Coles, 2002).

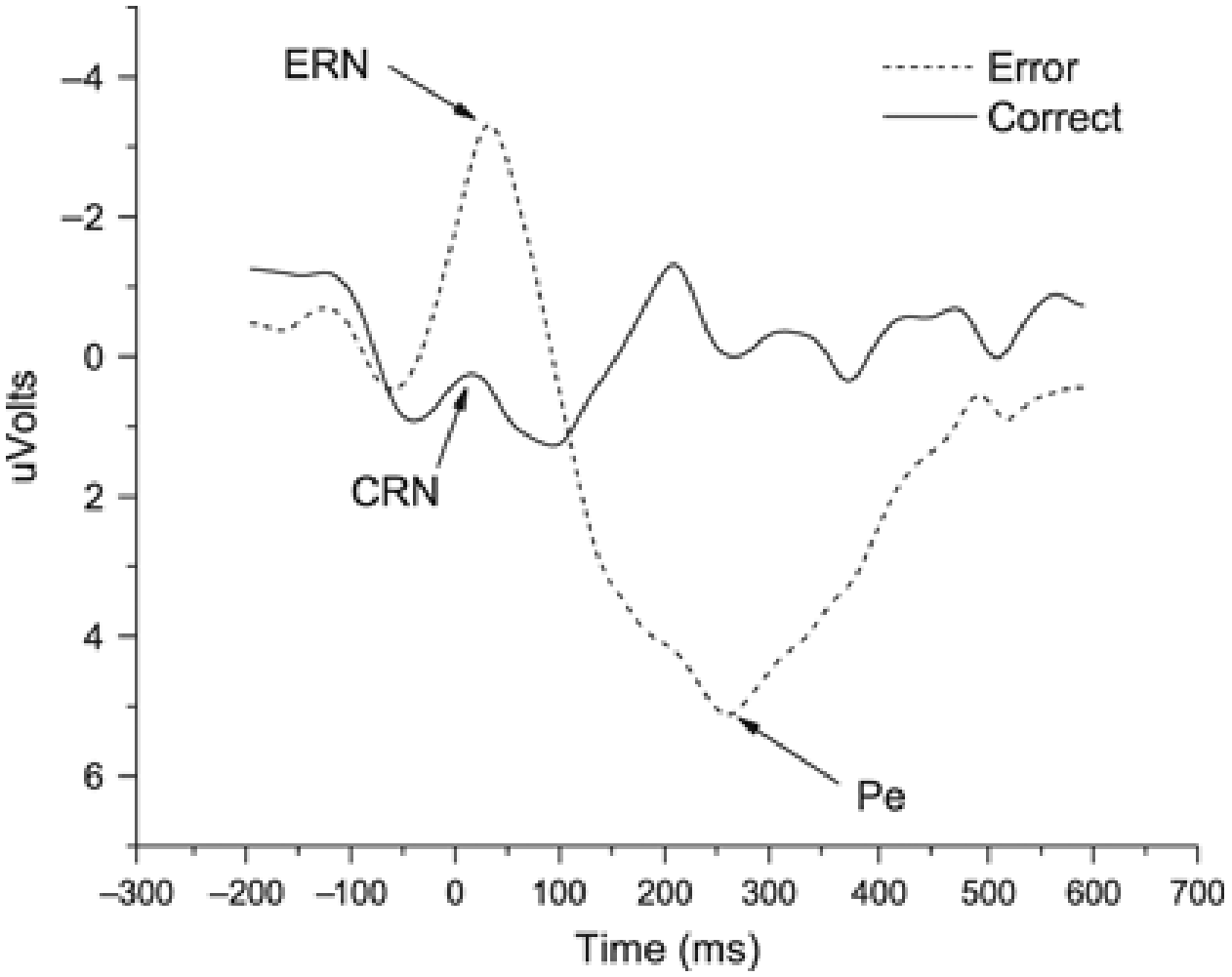


Figure 4: Averaged response-locked ERP waveforms for both error-related negativity (ERN), correct-related negativity (CRN) and error-related positivity (Pe) responses. Figure taken from Simons, 2009.

1.5: Dopaminergic reward prediction errors

One of the sources of ERN is argued to be reward prediction errors (Holroyd & Coles, 2002). According to this view, the ERN is produced by the impact of reward prediction error signals to the ACC via the mesencephalic dopamine system, which starts in the ventral tegmental area (VTA) and goes to the prefrontal cortex (PFC) (see Figure 5). The dopamine neurons in this system produce a dopaminergic reward prediction error (dRPE); which is the discrepancy between what reward was expected and what reward was received. Neurons send a rapid signal that covers all three possible scenarios in predicting a reward: that the reward was better than expected (a positive prediction error); that the reward was exactly as expected (no prediction error); or that the reward was less than expected (a negative prediction error) (Schultz, 2016). For example, if you were told you would receive 100 dollars to read this thesis, and received 200 dollars instead, you could experience a positive prediction error. Whereas, if you only received 20 dollars, you would experience a negative prediction error.

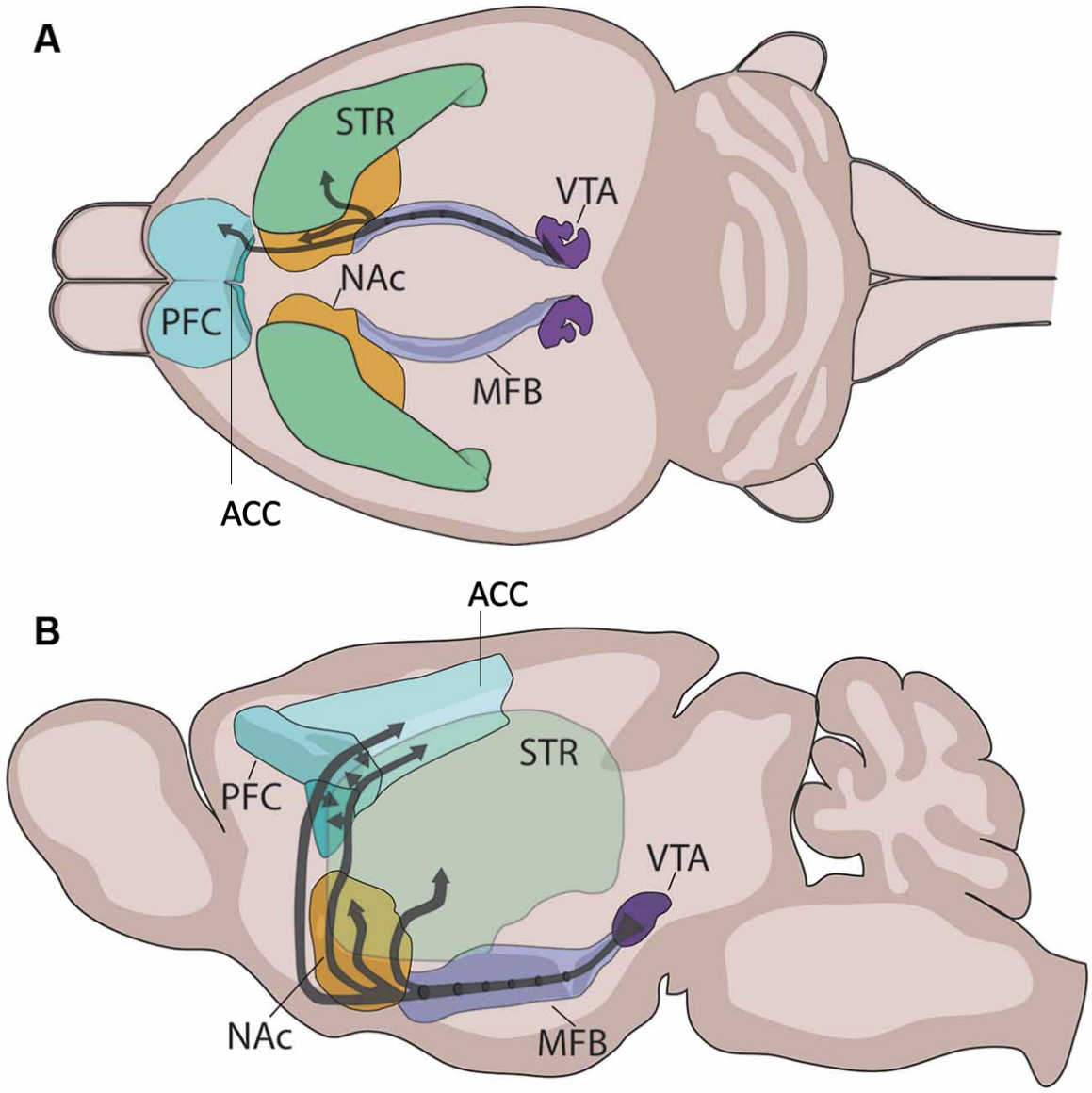


Figure 5: The main components of the mesencephalic dopamine system as seen in a mouse brain. Including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), striatum (STR), ventral tegmental area (VTA), nucleus accumbens (NAc) and medial forebrain bundle (MFB). Figure adapted from Reynolds & Flores (2021).

These dopaminergic error signals are projected to the ACC to adjust behavior. It is thought the ERN is generated when a negative dopaminergic error signal disinhibits the apical dendrites of motor neurons in the ACC, but no ERN is produced when these dendrites are inhibited by a phasic increase in activity of mesencephalic dopaminergic neurons following correct responses (Holroyd & Coles, 2002; Yasuda et al., 2004).

To further understand this process, we can look at the actor-critic framework (Konda & Tsitsiklis, 2000), which is a reinforcement learning algorithm that combines elements of both value-based and policy-based methods. It aims to find an optimal policy for decision-making in a given environment. In the actor-critic framework, there are two main components: the actor and the critic. The actor is responsible for selecting actions based on the current policy, whereas the critic evaluates the chosen actions and provides feedback on their quality. In this case, the ACC can be considered as the "critic" component. When an error is detected, a negative dopaminergic error signal is transmitted to the ACC, triggering a response adjustment.

A complementary framework that may offer new insights was introduced by Shenhav et al. (2013), and is referred to as the expected value of control theory. This theory states that the dorsal anterior cingulate cortex (dACC) integrates information concerning the potential rewards and costs associated with a control-demanding task. This integration enables the estimation of a specific quantity referred to as the expected value of control (EVC). Shenhav et al., (2013) found that the dACC calculates this value to assess the feasibility of investing control in a task. By estimating the EVC, the dACC determines whether it is worthwhile to allocate cognitive control, how much control should be assigned, and how to prioritize competing tasks. This information

guides the selection of tasks and the allocation of the appropriate level of cognitive control to effectively perform the chosen task.

Some research (Vlamings, 2008; Sokhade et al., 2010), has shown that individuals with ASD may have impairments in the brain regions associated with error processing, such as the ACC and the ERN component of the ERP. These neural abnormalities contribute to the altered error monitoring observed in individuals with ASD. Sokhade et al., (2010) and Vlamings (2008) show that the ERN and the Pe component of ERP were substantially decreased in children with ASD as compared to typical developing controls. In particular the amplitude of ERN was less negative and latency of both ERN and Pe were prolonged in the ASD group as compared to the typically developing children.

Research suggests that individuals with OCD show abnormalities in error processing, also in the ACC and the ERN (Johannes et al., 2001; Grützmann, 2016; Carrasco et al., 2013). They may exhibit enhanced error sensitivity, with a heightened neural response to errors compared to individuals without OCD. This heightened response to errors may contribute to the intense distress and the urge to engage in compulsive behaviors to rectify or prevent errors. Heightened error-processing, as indicated by an increased amplitude of ERN, shown by Mathews et al., (2012) is arguably the most reliable neurocognitive biomarker of OCD.

The relationship between reward prediction errors, dopaminergic signaling, and the generation of the ERN provides insights into the neural mechanisms underlying error processing and behavioral adjustments. By detecting and responding to negative prediction errors, the ACC and associated brain regions contribute to the monitoring and evaluation of performance outcomes, facilitating adaptive changes in behavior.

Chapter 2: Objectives, Hypothesis, and Importance

2.1: Objective

The objective of this study is to investigate the presence of metric error monitoring capabilities in mice by utilizing their nose-poke rate into a food hopper as a measure of confidence, or higher expectation of reward. To achieve this, a temporal task was employed, wherein mice were trained to press a lever for a target duration. The measurement of interest was the lever press duration and the corresponding rate of nose-poking into the food hopper, as food reinforcement was delivered only when the mice successfully pressed the lever for a duration longer than the specified target. By analyzing the relationship between the nose-poke rate and the veridicality of the time productions, this research aims to determine if mice exhibit metric error monitoring abilities.

2.2: Prediction

Under the metric error monitoring framework, I hypothesized that mice would emit higher rates of nose-poking in trials with TP around the target duration compared to short temporal productions.

2.3: Significance

We rely on error monitoring immensely in our daily lives to monitor and adapt our behaviours. Error monitoring research plays a crucial role in understanding and enhancing various aspects of cognition, behaviour, and performance. This thesis aims to investigate the temporal error processing abilities in mice, an essential step toward unraveling the neural

mechanisms involved in error monitoring and advancing our knowledge of these cognitive processes. By studying temporal processing in mice, we can gain insights into the fundamental principles of metric error monitoring, elucidate the neural networks involved, and uncover potential therapeutic implications for disorders related to temporal processing. Dysfunction in error monitoring occurs in neurological disorders such as autism spectrum disorder (ASD) (e.g. Doenyas et al, 2019, 2020) and obsessive compulsive disorder (OCD) (e.g., Grützmann, 2016; Carrasco et al., 2013; Fitzgerald & Taylor, 2015). Therefore, studying temporal error monitoring in non-human animals can facilitate the development of novel interventions and treatments for disorders such as ASD and OCD.

Moreover, investigating temporal processing in a non-human animal model enables comparative analyses and provides a valuable foundation for understanding the evolution and universality of temporal cognition across species. The understanding of magnitude representations, including overlaps, and the processing of uncertainty and errors in rodents is currently very limited. This research aims to elucidate the information-processing and neural bases of the metric capacity of non-human animals, integrating concepts from interval timing and error monitoring. By conceptually integrating these domains, the current research will have transformative and consolidatory impacts on comparative and behavioral neuroscience.

The outcomes of this study will not only contribute to our understanding of these cognitive abilities but also hold translational value. The insights gained can be translated into methods that may promote behavioral adaptation in central nervous system disorders characterized by cognitive and behavioral rigidity, such as OCD and ASD. Thus, the findings of

this research have the potential to bring about meaningful changes in clinical applications and have practical implications in the field of cognitive and behavioral neuroscience.

Chapter 3: Materials and Methods

3.1: Materials

3.1.1: Subjects

Male C57BL/6 mice (N = 16) were obtained and bred at the Animal Holding Facility Bannatyne campus of the University of Manitoba (Winnipeg, Manitoba) at 8 weeks of age and held in the Animal Holding Facility of the University of Manitoba at Fort Garry campus. The mice were food deprived to 85% of their ad-lib weight three days prior to the beginning of the experiment. All experiments were conducted during the light phase on weekdays, mice were taken to experimental sessions approximately at the same time of the day for one session, and daily sessions were one hour long. The mice were group-housed in individually ventilated cages (IVC) in pairs.

3.1.2: Apparatus

The experiment was performed in modular operant boxes (ENV-307W; Med Associates Inc.) with a stainless steel grid floor (see Figure 6). The operant box configuration included one lever (ENV-312-3W) in between two receptacles (ENV-303M) that can be lit by LEDs (ENV-303RL-3) for local stimuli. The head entries to the receptacles were detected by infrared beam break detectors (ENV-303HDA). The operant box also included a speaker (ENV-324M) and a house light (ENV-315M-LED). For reinforcement, dustless full-grain 20 mg pellets (F0071; Bio-Serv) were delivered via pellet dispensers (ENV-203–20). Operant boxes were placed in sound-attenuating chambers. Fans in each cubicle were used to ventilate the cubicle and create a white noise to muffle outside noise.

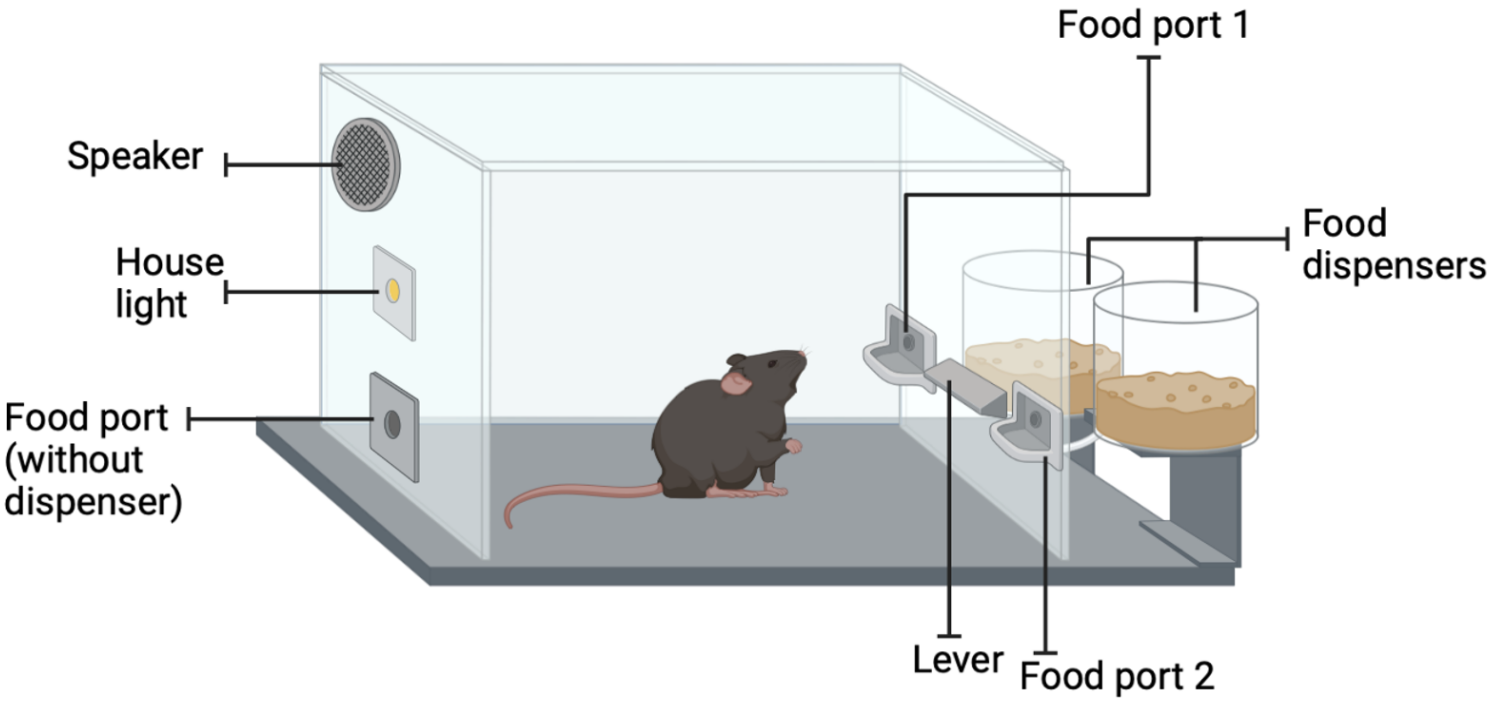


Figure 6: Operant box configuration. (Designed on biorender.com)

3.2: Methods

3.2.1: Pretraining

1. *Magazine training (2 consecutive sessions)*: Mice were first familiarized with the food/reward dispenser port. The trial began after a random inter-trial interval (ITI) from 10 to 15 seconds in steps of 1 second. The light of a randomly chosen reward port was turned on at the same time as a pellet drop. The light stayed on for 2 seconds. If the pellet was retrieved by the mouse, a new trial began. If the pellet was not retrieved, a new trial began after 7 seconds. The session ended when 40 pellets were released.
2. *Nose-poke training:* Mice were trained to nose-poke in the correct dispenser port (light on) in order to receive a reward. The trial began after an ITI from 60 to 90 seconds in steps of 5 seconds, and the light in the given reward port stayed on for 5 seconds per trial. Sessions were one-hour long. Nose-poke training ended, and mice advanced to the next training stage (*lever press training*) when they successfully collected rewards in >80% of trials in two consecutive sessions.
3. *Lever press training:* Mice were trained to press a lever resulting in the activation of the dispenser port light. The lever was inserted after an ITI from 60 to 90 seconds in steps of 5 seconds. The lever was retracted after a lever press was made or after 5 seconds had passed and a new trial started. The port in which the light turned on was randomly chosen with an equal probability between the two ports. Mice then needed to nose-poke into the dispenser port with the light on to receive a reward. The session ended after one hour. Lever press training was complete, and mice advanced to the next

training stage (*duration and precision training*) when they successfully collected rewards in >80% of trials in two consecutive sessions.

3.2.2: *Duration training*

The mice were trained to press down a lever for the required minimum amount of time, or target duration (T) of 1 or 2 seconds (see Figure 7). On a given trial, the time interval that a mouse produced was referred to as temporal production (TP). Training began with T = 0.5s, where mice received a reward only if they produced a TP of at least 0.5s. T increased logarithmically (0.5, 1, 2) to the final *T* of 1 or 2 seconds. Mice progressed to the next *T* after achieving 65% performance or completing a maximum of 20 sessions at one duration.

3.2.3: *Error monitoring test*

After duration training, mice underwent error monitoring testing. After an intertrial interval (ITI) of 16-32 seconds, the lever was inserted into the operant box, and the mice were required to press down the lever for the required target duration (T) of 1 or 2 seconds in order to receive a reward. Notably, each trial consisted of a single response.

During testing, one of the hopper lights was chosen at random to be activated for a variable amount of time ranging from 2 to 8 seconds, regardless of whether the mouse's response was correct or incorrect. The rate of nose-pokes into the correct hopper during the variable response window was recorded. If the response was correct and the mouse was poking its nose in the correct hopper, a reward was delivered at the end of the variable response window.

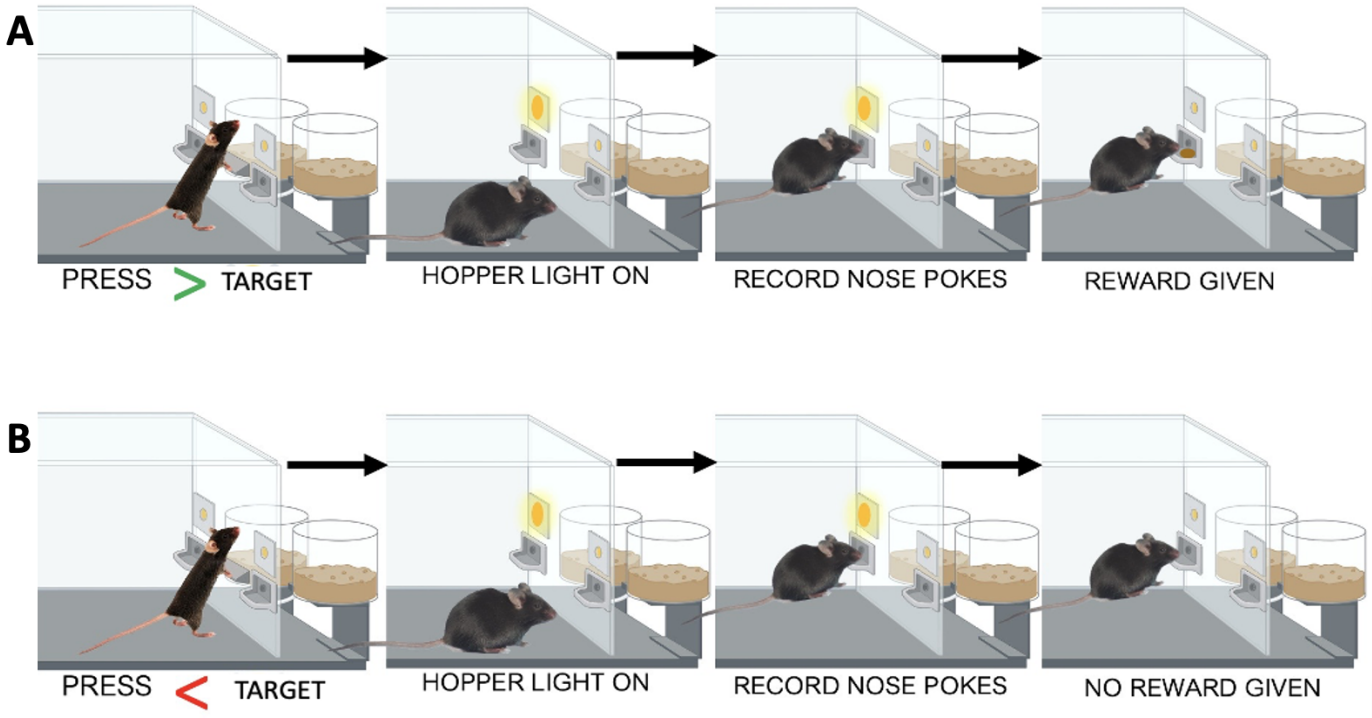


Figure 7: A) Experimental design in correct trials B) Experimental design in incorrect trials. (Designed with BioRender.com)

3.3: Data analysis

All data analysis was performed using custom MATLAB and R scripts.

3.3.1: Time production analysis

The mean and standard deviations of temporal productions (TP) were calculated for all sessions for each mouse as measurements of central tendency and variability, respectively. By examining the mean and standard deviations of TP, we gained a comprehensive understanding of the mice's ability to accurately and precisely estimate and reproduce specific durations. Thus, TP estimates served as quantitative indicators of the mice's temporal judgment and their ability to meet the task criteria.

Each subject's temporal production data were fit using the exponential Wald mixture distribution (see Equation 2). In Equation 2, p is the proportion of the exponential distribution (1 − p is the proportion of the Wald distribution), **γ** is the rate parameter of the exponential distribution, $\boldsymbol{\mu}$ is the mean, and $\boldsymbol{\lambda}$ is the shape parameter of the Wald distribution.

$$f(x \mid p,\gamma,\mu,\lambda) = p(\gamma e^{-\gamma x}) + 1 - p)\sqrt{\frac{\lambda}{2\pi x^3}}\, e^{-\frac{\lambda(x-\mu)^2}{2\mu^2 x}}, \quad 0 \le p \le 1 \tag{2}$$

Following, responses were plotted using the cumulative dentisty function (CDF) of this mixture distribution. These plots depict the cumulative distribution of lever presses across different temporal productions. In these plots, the x-axis represents the temporal production in seconds, ranging from the minimum target duration to the maximum target duration. The y-axis

represents the cumulative density, which indicates the proportion of lever presses performed up to a given temporal production. The cumulative density (y-axis) is calculated by summing the frequencies of lever presses for each temporal production point and dividing it by the total number of lever presses. The steepness or slope of the curve indicates the rate at which the mice accumulated lever presses as the temporal production increased. A steeper slope suggests a more rapid accumulation of lever presses, while a flatter slope indicates a slower accumulation (higher and lower temporal precision, respectively).

3.3.2: Nose-poke rates

After the lever was released, the rate of nose-pokes into the food hopper during the variable response window with the hopper light on was recorded for all sessions for each mouse. In each trial, a single nose poke ratio was recorded. This period was crucial for observing the mice's behavior following their temporal productions and lever presses. The rate of nose-pokes during this specific timeframe served as a proxy for confidence. Methods using response rate as a proxy for confidence have been used in previous studies (e.g., Blough, 1967; Yi, 2009). Blough (1967) used response rate as a measure of pigeons' certainty that a reinforced stimulus had been presented. A series of light stimuli with different wavelengths were presented, and pigeons were reinforced for pecking only when the wavelength was 582 nm. A low number of responses during a trial suggested that the pigeon was "certain" that the present stimulus was not the 582-nm stimulus. A similar measure was used by Yi (2009). Rats were reinforced for responding on a lever labeled "long" after a long interval and responding on a

lever labeled “short” after a short interval. On an unreinforced cycle, the presentation of a stimulus was followed by a 10-s time window. The number of “long” and “short” responses that occurred within this time window was used as a measure of the rats’ certainty or confidence in the duration of the presented interval. In our study, the nose-poke rate was calculated by dividing the total number of nose-pokes by the duration of the response window. This normalization allowed us to compare the nose-poking behaviors across different mice, sessions, and trials/temporal productions, providing a standardized metric for analysis of “confidence”.

3.3.3: Linear mixed-effects

In order to address sample dependency caused by multiple observations per animal across sessions, we employed linear-mixed effects models (LME). LME is a type of regression model that accommodates data with multiple levels. The linear mixed-effects model takes into account both fixed effects (systematic effects) and random effects (individual-specific effects or effects due to clustering). The fixed effects capture the relationships between the predictors and the response variable at the population level, while the random effects account for variability among individuals.

The general formulation of LME (Laird & Ware, 1982) is as follows:

(3)

$$Y = X\beta + Zb + \varepsilon$$

In this equation, Y represents the dependent variable (response variable). X represents the fixed-effects design matrix, which includes the predictor variables (independent variables - X) and their coefficients (β) that represent the fixed effects. Z represents the random-effects

design matrix, which includes the random effects (b) and their associated variance-covariance structure. ε represents the residual error term. It captures the variability in the response variable Y that is not accounted for by the fixed effects (Xβ) and random effects (Zb). The term ε includes all other factors or sources of variation that are not explicitly included in the model. It encompasses various unobserved or unmeasured factors, such as measurement error, uncontrolled variables, and inherent randomness in the data. It represents the discrepancy between the predicted values based on the fixed and random effects and the actual observed values of the response variable.

In our specific analysis, we used the "lme" function in R to fit the linear mixed-effects model. The response variable in our model was the nose-poke ratio, which represents the frequency of nose-pokes into the food hopper per unit time. We included the following predictor variables: temporal production, session, trial, session*trial (interaction between session and trial), and hopper accuracy (if the mouse went to the correct hopper directly after releasing the lever). The random effects were accounted for by specifying the random term as ~1|subject, indicating that we included random intercepts for each individual mouse in the study. This accounts for the individual-specific effects or clustering that may exist within the data. We used the maximum likelihood (ML) method to estimate the model parameters. The ML method is commonly employed in LMEs and aims to find the parameter estimates that maximize the likelihood of observing the data given the model.

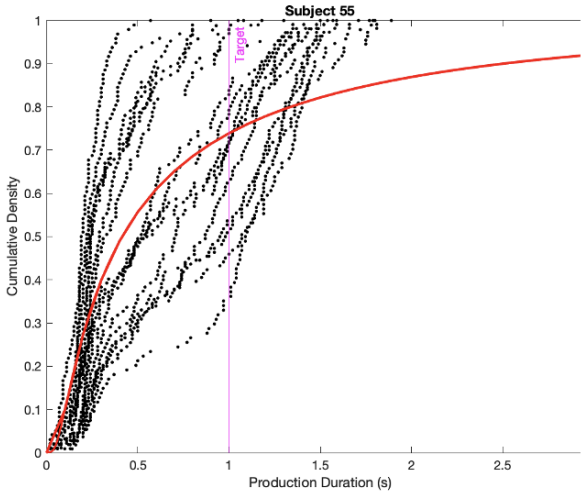
Chapter 4: Results

4.1: Mice are near-optimal timers

The mice underwent training to perform lever presses for specific target durations (T), starting at 0.5 seconds and logarithmically increasing to a final target duration of either 1 or 2 seconds. In order to advance to the next target duration, mice were required to achieve “steady state performance” (a performance level of 65% or higher) or complete 20 sessions at the given duration. To assess the mice's performance and visually illustrate the temporal production of each mouse, cumulative density plots were generated for each session for each mouse, shown in Figures 8 and 9, depicting the distribution of lever presses. Additional histogram representations can be found in supplementary Figures 1 and 2.

The average of the estimated mean production durations (experimental μ) for T = 1 second, obtained from the Wald proportion (excluding exponential proportion) of individual fits was 1.0403 seconds.

The average of the estimated mean production durations (experimental μ) for T = 2 seconds, obtained from the Wald proportion (excluding exponential proportion) of individual fits was 2.1853 seconds.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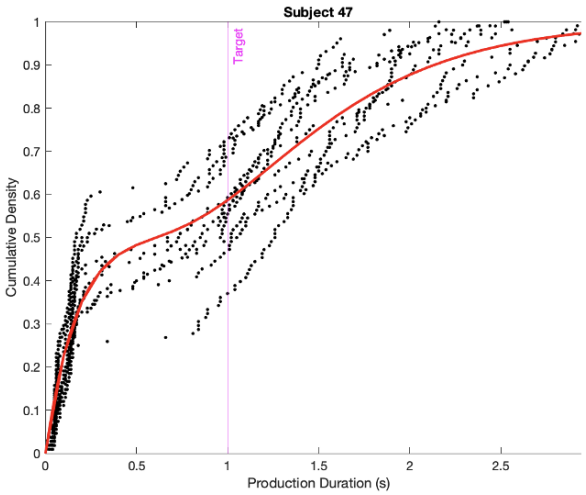
Production Duration (s)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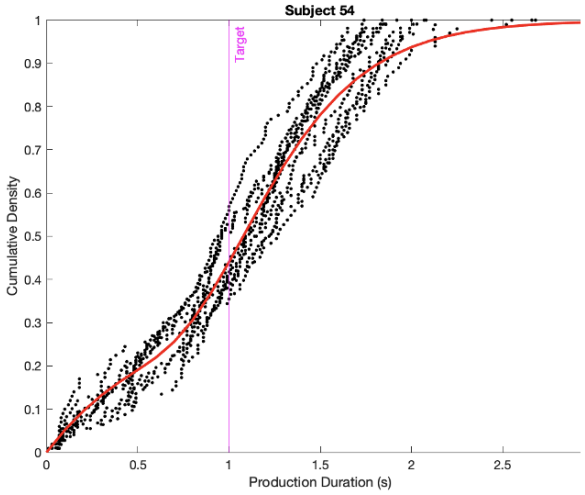
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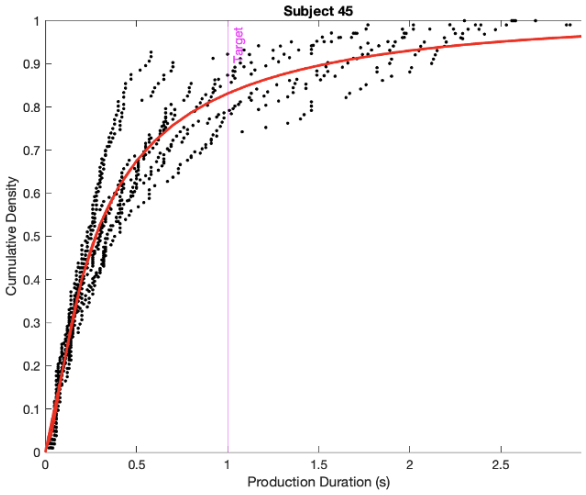
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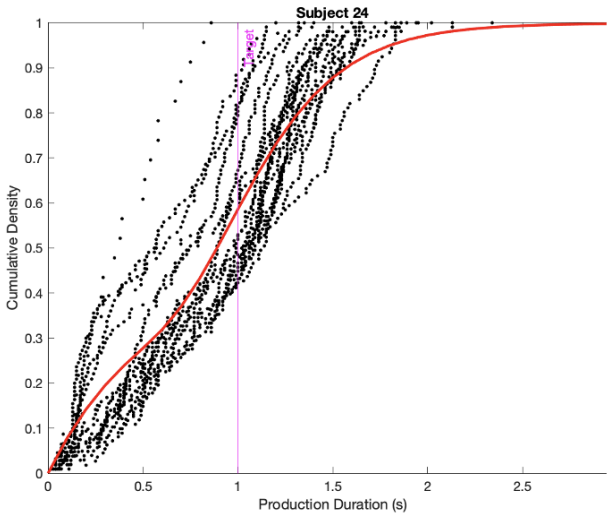
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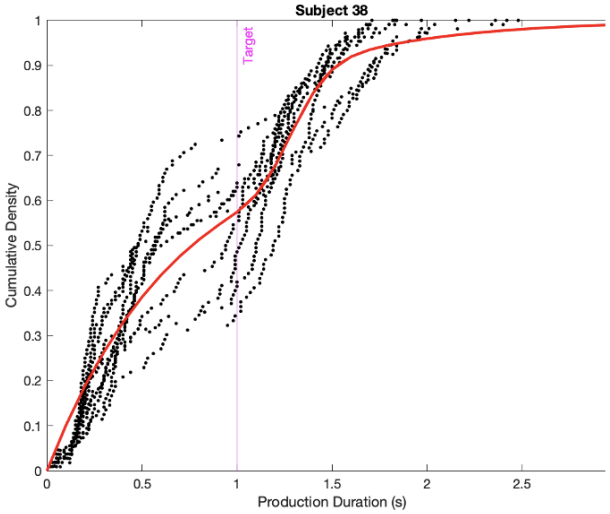
Production Duration (s)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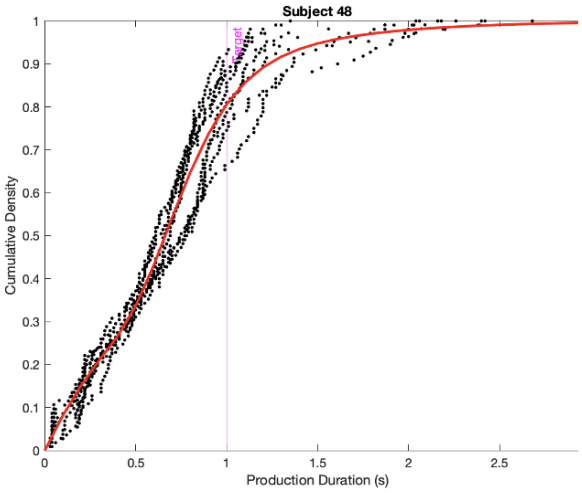
Production Duration (s)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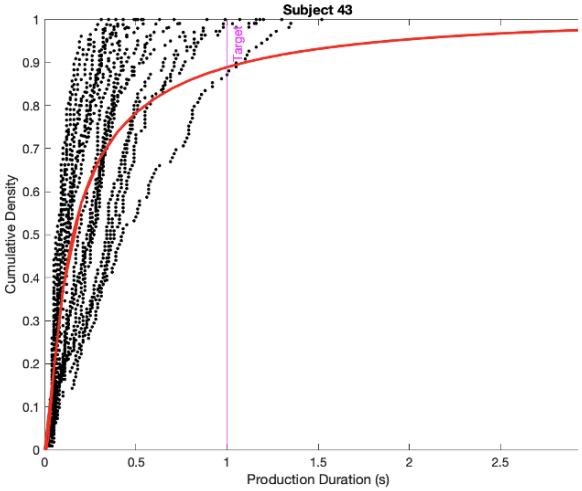
Cumulative Density
Production Duration (s)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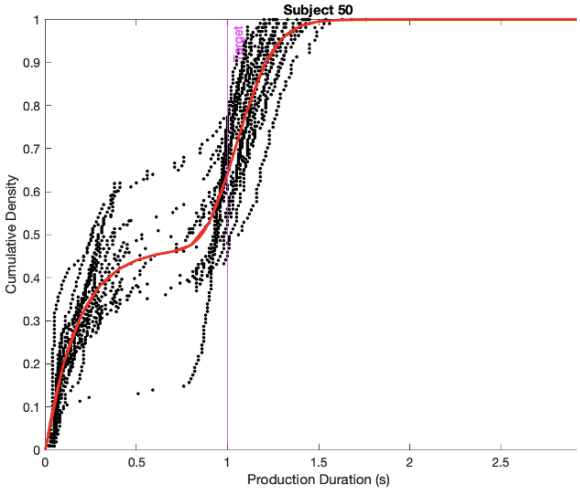
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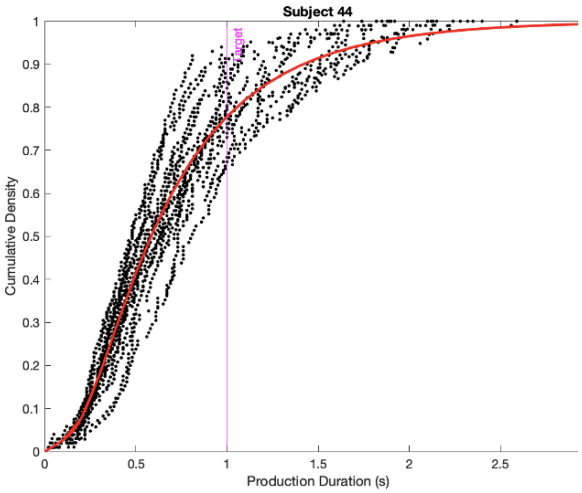
Cumulative Density
Production Duration (s)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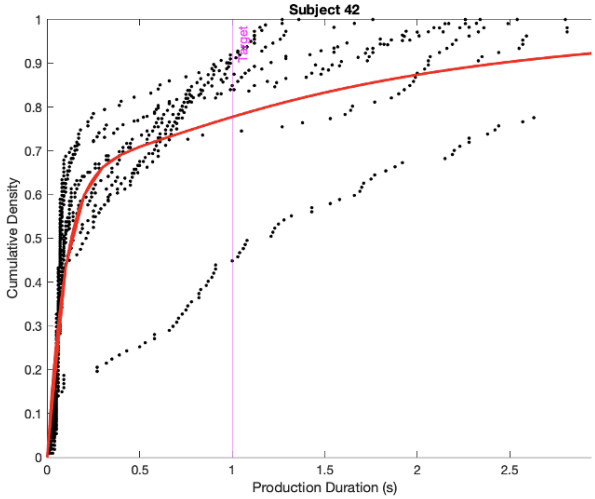
Target
Cumulative Density
Production Duration (s)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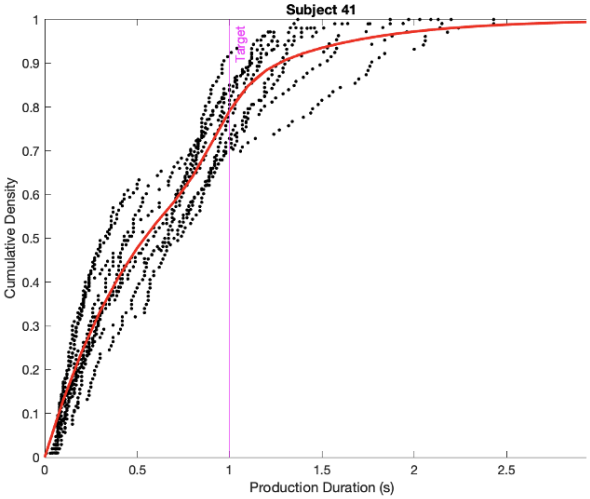
Production Duration (s)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Production Duration (s)

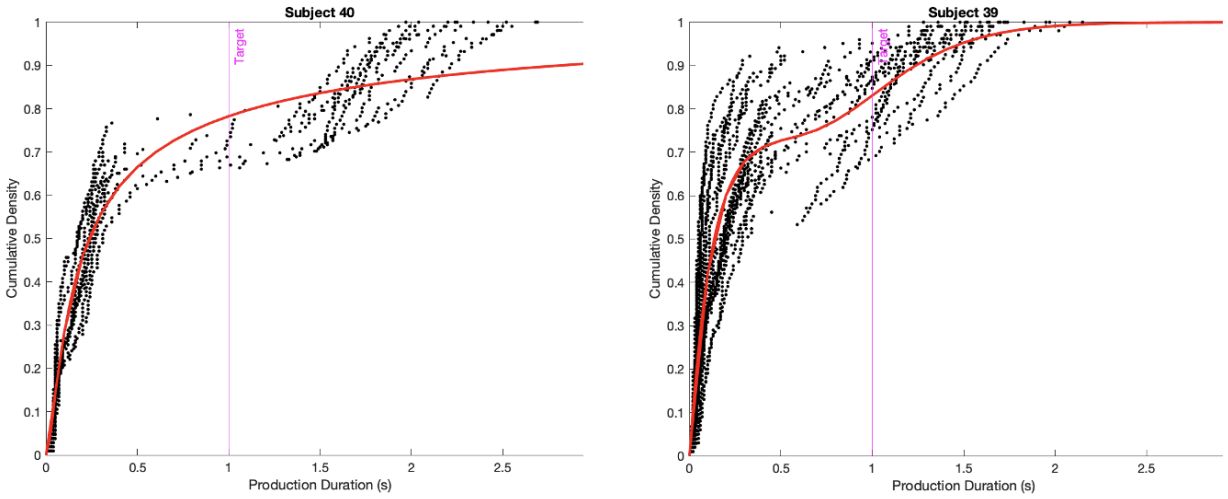
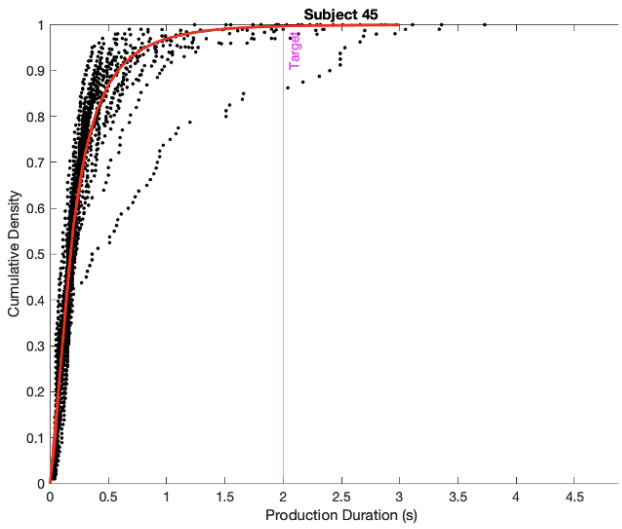


Figure 8: Cumulative density plots illustrating the temporal production of mice for T = 1 second. Each plot represents an individual mouse and includes data from all testing sessions. Plots were generated by fitting the duration of lever presses in each trial across all sessions. The x-axis represents the production duration (in seconds), while the y-axis represents the cumulative density. The red line represents the fitted cumulative density of the mixture distribution function based on the data. The target duration is indicated by the magenta line.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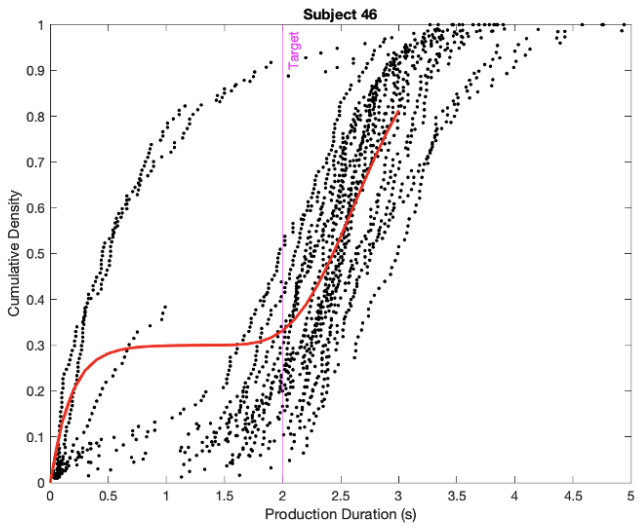
Cumulative Density
Production Duration (s)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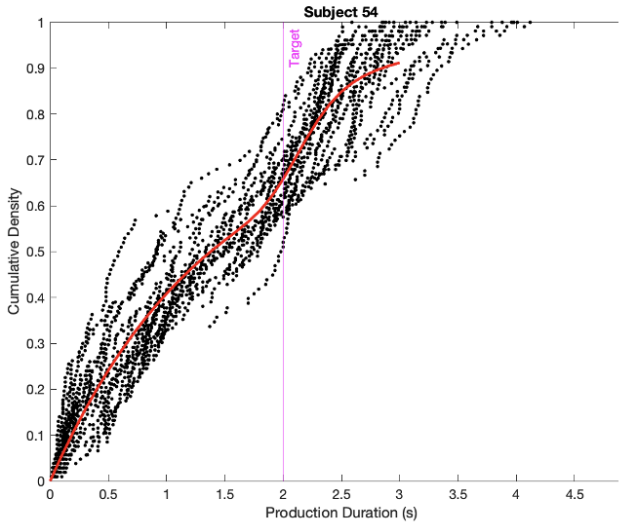
Production Duration (s)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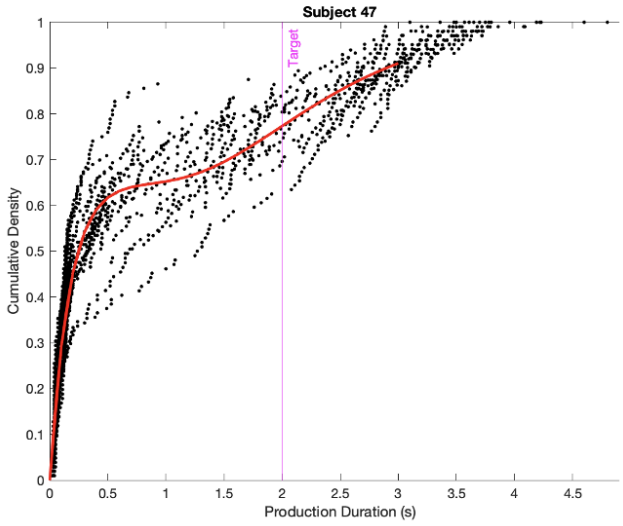
Production Duration (s)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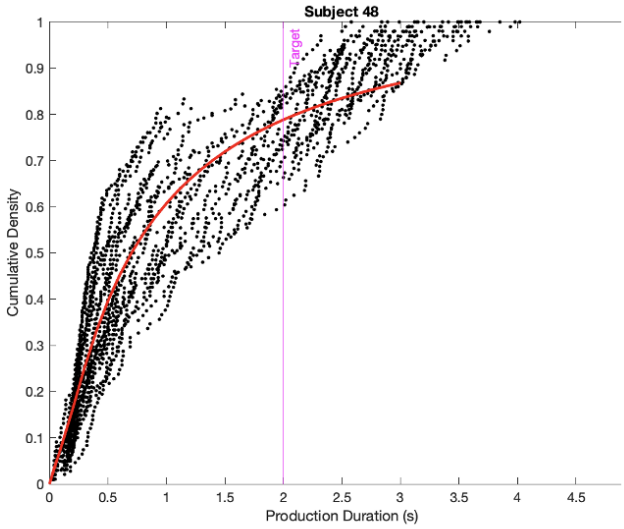
Target
Cumulative Density
Production Duration (s)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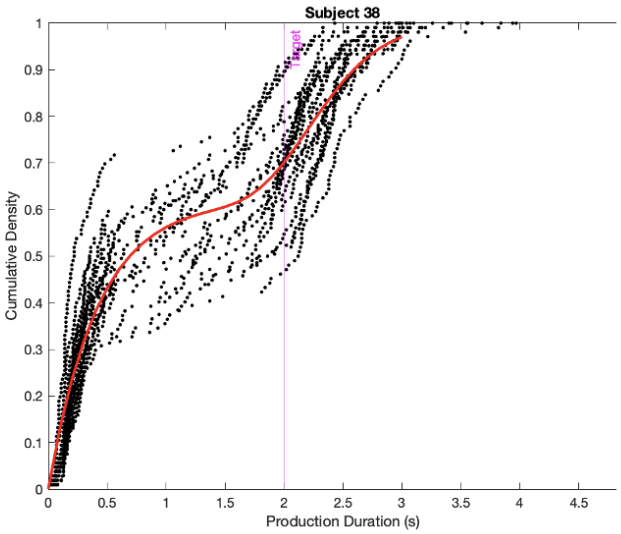
Cumulative Density
Production Duration (s)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Target
Cumulative Density
Production Duration (s)

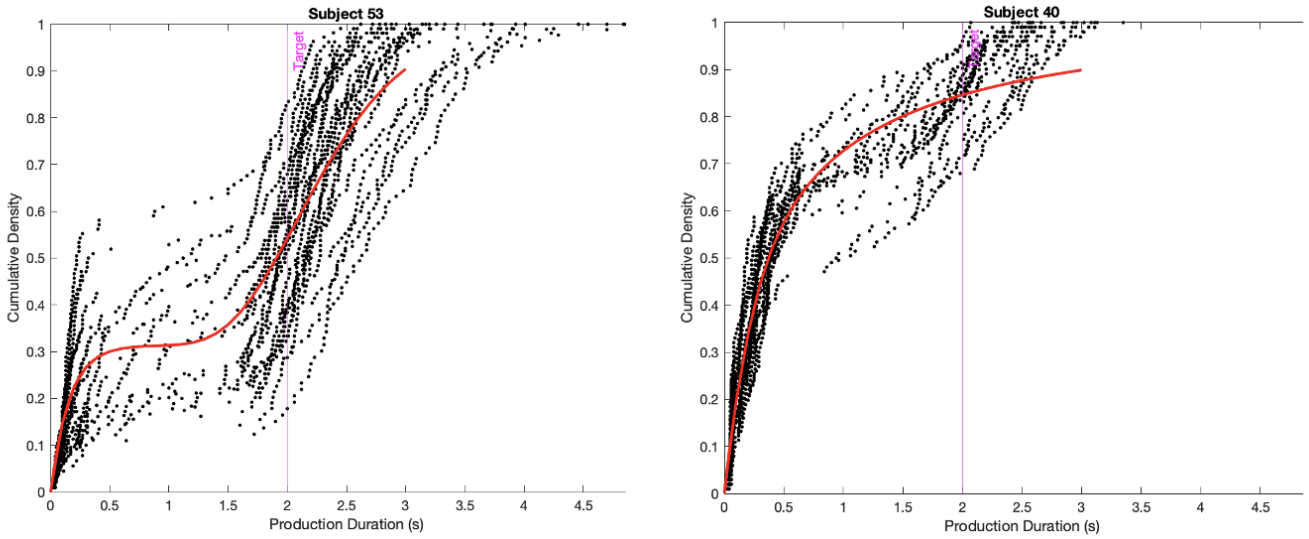

Figure 9: Cumulative density plots illustrating the temporal production of mice for T = 2 seconds. Each plot represents an individual mouse and includes data from all testing sessions. Plots were generated by fitting the duration of lever presses in each trial across all sessions. The x-axis represents the production duration (in seconds), while the y-axis represents the cumulative density. The red line represents the fitted cumulative density of the mixture distribution function based on the data. The target duration is indicated by the magenta line.

4.2: Mice can monitor their temporal errors

We aimed to evaluate the MEM performance of the mice by examining their nose-poke ratios in relation to their temporal productions. The underlying assumption was that if the mice possessed MEM abilities and could accurately judge whether their temporal productions were close to the task criterion for obtaining a reward, we would expect to observe higher rates of nose-poking in trials where the temporal productions were close to the target duration. This increased nose-poking rate was considered a proxy for the mice's confidence, as it indicated their anticipation of receiving the reward. By examining the relationship between nose-poke ratios and temporal productions, we could gain insights into the mice's MEM abilities and their level of confidence in their temporal productions.

Two mice were tested exclusively at T = 1 second for 20 sessions, whereas six mice were tested exclusively at T = 2 seconds for 20 sessions. A separate group of eight mice underwent testing at T = 2 seconds for 20 sessions and were then tested at T = 1 second for 10 sessions.

We used a linear mixed-effects model (LME) to examine the relationship between the nose-poke ratio in mice and the predictor variable of temporal production. The LME model employed in this study facilitated the examination of both fixed effects, specifically the temporal production predictor variable, and random effects, accounting for individual variability related to the subject. This comprehensive approach allowed us to explore the influence of temporal production while considering the inherent variability among subjects in our analysis.

To ensure data quality and reduce the influence of outliers, we applied an exclusion criterion. Specifically, we removed observations where the temporal production exceeded the

mean plus three times the standard deviation of the temporal production. This step helped to eliminate extreme values that could potentially bias the analysis.

Our results revealed several important findings. Our results for T = 2 seconds, shown in Figure 10 and Table 1 show a significant positive predictive relation between temporal production and nose-poke rate (0.1482484, $p < 0.0001$). This indicates that as the temporal production increased, the nose-poke ratio increased significantly. This suggests that mice displayed higher levels of confidence and anticipation for a reward when their temporal production was close to the task criterion.

In sessions with a target duration of 1 second (T = 1), shown in Figure 11 and Table 2, we again observe a significant positive relationship between temporal production and nose-poke ratio (0.3382775, $p < 0.0001$).

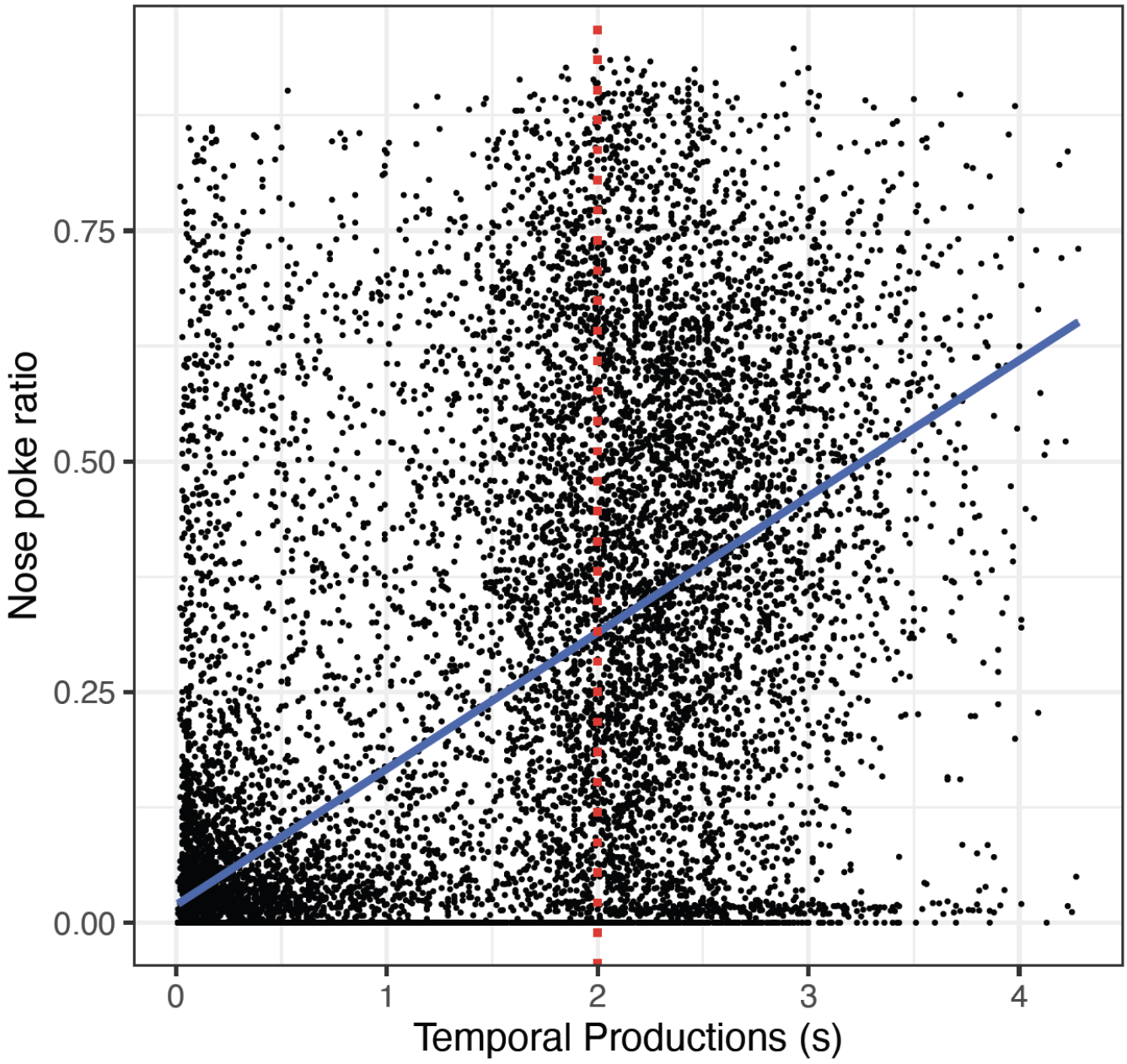

Figure 10: Relationship between nose-poke ratio and temporal production with target duration (T) = 2 seconds. Data were collected in 14 mice (n=14) for 20 sessions each. The x-axis represents the temporal production, indicating the actual duration of the lever press produced by the mice. The y-axis represents the nose-poke ratio, reflecting the frequency of nose-pokes into the food hopper. As the temporal production approaches the target duration of 2 second, the nose-poke ratio shows a significant increase, indicating higher confidence and anticipation for the expected reward.

Table 1: Summary of Linear Mixed-Effects Model Results for Target Duration (T) = 2 Seconds.

RANDOM EFFECTS	**Standard deviation**
Subject (intercept)	0.07298724
Residual	0.1861219

FIXED EFFECTS	**Value**	**Standard error**	**DF**	**t-value**	**p-value**
Intercept	0.0198097	0.02325550	17044	0.85183	0.3943
Temporal production	0.1482484	0.00153646	17044	96.48695	0.0000

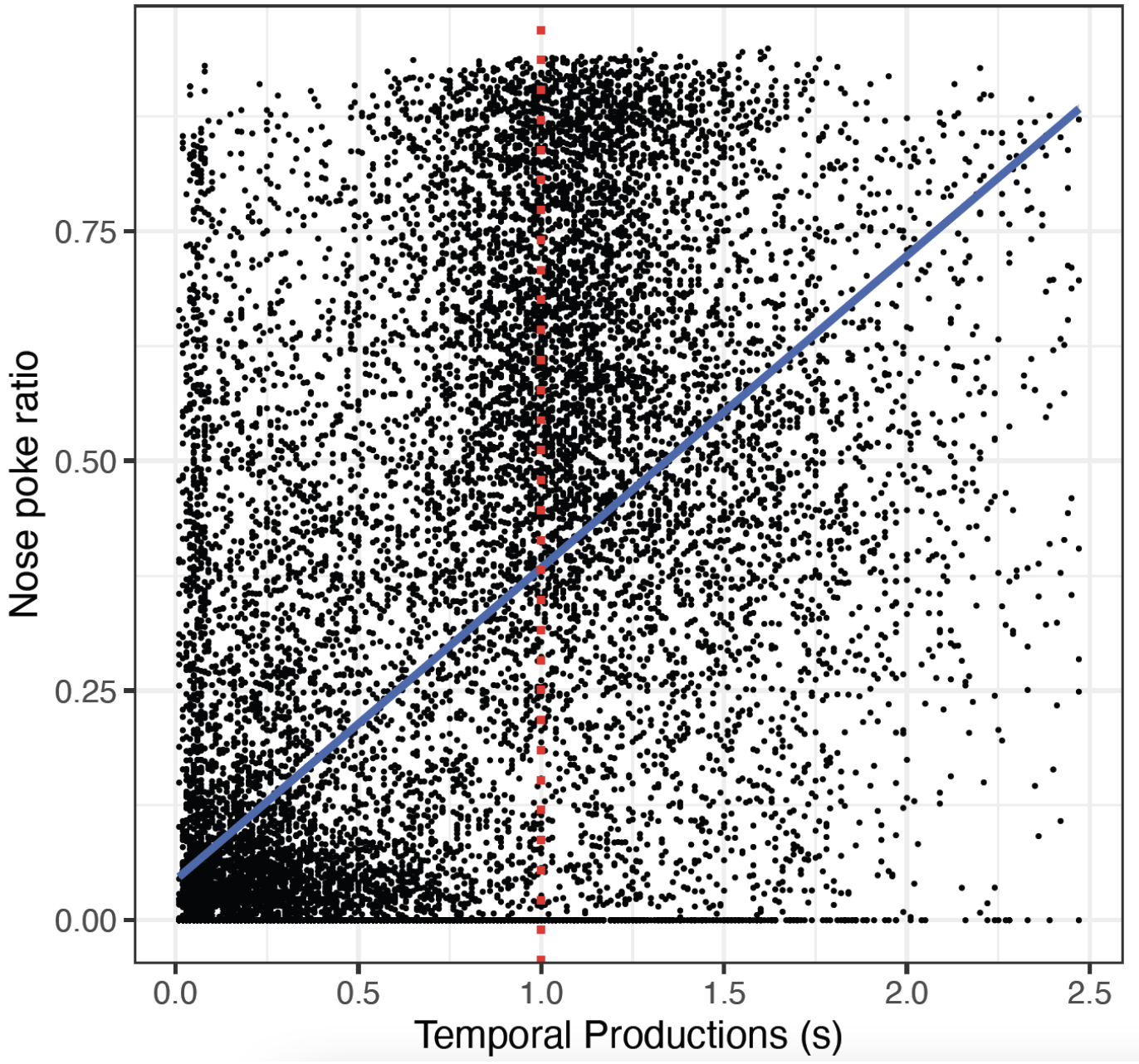

Figure 11: Relationship between nose-poke ratio and temporal production with target duration (T) = 1 second. Data was collected in 10 mice (n=10) for 20 sessions each. The x-axis represents the temporal production, indicating the actual duration of the lever press produced by the mice. The y-axis represents the nose-poke ratio, reflecting the frequency of nose-pokes into the food hopper. As the temporal production approaches the target duration of 1 second, the nose-poke ratio significantly increases, indicating higher confidence and anticipation for the expected reward.

Table 2: Summary of Linear Mixed-Effects Model Results for Target Duration (T) = 1 Second.

RANDOM EFFECTS	**Standard deviation**
Subject (intercept)	0.1040119
Residual	0.2222503

FIXED EFFECTS	**Value**	**Standard error**	**DF**	**t-value**	**p-value**
Intercept	0.0359138	0.027923907	19744	1.28613	0.1984
Temporal production	0.3382775	0.003174076	19744	106.57511	0.0000

Chapter 5: Discussion

5.1: Mice can monitor their temporal errors

The primary aim of this study was to investigate metric error monitoring (MEM) abilities of mice. We adapted methods from previous studies (e.g., Blough, 1967; Yi, 2009) that used response rate as a proxy for the animals' certainty and confidence. For example, in Blough's study (1967), pigeons were reinforced for pecking when a stimulus was shown. A low response rate indicated that the pigeon was "certain" that the target stimulus was not shown. Similarly, Yi (2009) measured certainty in rats by reinforcing lever responses based on short or long intervals. The number of "long" and "short" responses reflected the rats' confidence in the duration of the presented interval. In the current study, mice were trained to depress a lever at least for a target duration in order to receive a reward in the food hopper. No reward was given when mice under-produced the minimum required target interval. During test trials, the rate of nose-pokes into the food hopper during a variable response window after releasing the lever was recorded as a measurement of the mice's confidence.

As hypothesized, we observed more vigorous nose-poking in trials with time productions (TP) close to the target duration compared to trials with TPs much shorter than the target duration. When the mice were confident with their TP, the frequency of their nose poking into the food hopper increased in anticipation of the expected reward. We observed when mice underproduce the target duration, they are not confident with their TP and do not expect a reward, therefore the frequency of their nose-pokes into the food hopper decreases significantly. This pattern held true for both 1-second and 2-second target durations. The LME

analysis, which accounted for both fixed effects and random effects, demonstrated a significant positive relationship between TP and nose-poke ratio. These findings were validated by the LME plot (see Figure 10 and 11), which visually displayed the trend of increasing nose-poke rates as TP values approached the target duration. **This finding demonstrates that mice possess the ability to discern, better than chance, whether their temporal performance is close to meeting the task criterion for reward. These results provide strong evidence supporting the existence of metric error monitoring abilities in mice.** Such abilities imply that mice may possess a level of self-awareness and possess the cognitive capability to monitor their own performance, which has significant theoretical implications for our understanding of animal cognition across different species. Previous studies have shown that rats and mice can exhibit similar metacognition-like behavior, further highlighting the cognitive mechanisms that allow animals to seek information in uncertain situations (Kirk et al., 2014), assess their own memory strength (Templer et al., 2017), make memory-guided decisions (Joo et al., (2021), and differentiate between their measurement error and external timing uncertainty (Kheifets et al., 2017).

5.1.1: Mice can monitor their temporal errors at varying durations

In our experimental design, we implemented two different durations of lever press, T = 1 second and T = 2 seconds, to investigate the mice's ability to perform temporal productions and error monitoring at varying time intervals. However, it is worth noting that not all mice were exclusively tested at one duration. Instead, we employed a varied approach where some mice were exclusively tested at 2 seconds, some exclusively at 1 second, and some experienced a switch from 2 seconds to 1 second. This strategic manipulation of durations was essential for

several reasons. By incorporating these two durations, we aimed to evaluate the mice's behavioral flexibility and their capacity to adapt to different temporal demands. Additionally, using two different durations enabled us to assess the mice's error monitoring capabilities across varying time frames. By incorporating a switch from one duration to another, we introduced a level of complexity that reflected real-life situations. Organisms often encounter dynamic environments where temporal demands can vary. This aspect of our experimental design allowed us to examine the mice's cognitive flexibility and their capacity to adjust their error monitoring processes to different time frames.

5.1.2: Significance of results for animal cognition

The discovery of MEM capabilities in mice has significant theoretical implications for our understanding of animal cognition.

Firstly, it challenges the notion that heightened cognitive processes, such as self-awareness and error monitoring, are exclusive to human cognition. The presence of error monitoring abilities in mice, along with the discovery of MEM in rats by Kononowicz et al., (2022), suggests that these cognitive processes may be more widespread across different species and are not limited to primates. Building upon that, the presence of heightened expectancy for rewards in mice raises intriguing questions about the evolutionary origins and functional significance of these abilities. Understanding the extent to which animals possess these processes provides valuable insights into the adaptive value of performance monitoring and self-evaluation in differing environments. By evaluating and adjusting their cognitive processes, animals can optimize their decision-making, problem-solving, and learning,

ultimately enhancing their ability to navigate their surroundings and adapt to the challenges they encounter.

Furthermore, these findings have the potential to uncover therapeutic implications for disorders related to temporal processing and cognition. Dysfunction in error monitoring occurs in neurological disorders such as ASD and OCD. Therefore, a deeper understanding of the heightened expectation for rewards in non-human animals, as well as the identification of error monitoring capabilities in mice, as we found in our study, can contribute to the development of novel interventions and treatments for these disorders. By elucidating the underlying cognitive mechanisms and processes involved in the heightened expectation for rewards, we can potentially improve diagnostic approaches and therapeutic strategies for individuals affected by these conditions.

5.2: Previous MEM research

Our findings are in line with previous research (e.g., Akdoğan & Balcı, 2017; Duyan & Balcı, 2019, Doenyas, Mutluer, Genç, & Balcı, 2019; Kononowicz et al., 2019; Kononowicz & van Wassenhove, 2019) that show humans do have MEM abilities as they were able to judge the size and direction of metric errors, suggesting that the uncertainty in magnitude representations is accessible to the human cognitive system.

Before these pioneering findings in 2017 (Akdoğan & Balcı, 2017) regarding the magnitude and direction of errors, error monitoring studies relied on two-choice procedures (2AFC) that did not capture the full extent of error monitoring. These studies focused on simple binary choices, such as pressing one button versus another, and evaluated performance

accuracy based on correct or incorrect responses. Although these studies provided valuable insights into error detection and correction, they lacked the ability to assess the crucial metric component of error monitoring that we are interested in. The introduction of the magnitude and direction of errors as essential dimensions in error monitoring research has the potential to change our understanding of how organisms perceive and evaluate their own performance. In Akdoğan and Balcı's study (2017), participants were asked to reproduce target durations as accurately as possible. After each reproduction, participants were asked to rate their confidence in their temporal estimates retrospectively and to judge if their response time was shorter or longer than the target interval. Results of this study showed for the first time that humans can correctly keep track of the direction and magnitude of their errors in the reproduction of target time intervals.

As importantly, our results are in line with more recent research on rats (Kononowicz et al., 2022) that discovered that MEM is present in non-human animals. They conducted a study training the rats in a task where time intervals were produced by pressing or holding down a lever. The researchers categorized the temporal productions as small errors (close to the minimum duration) or large errors (much longer than the minimum duration). The rats received a different amount of pellet rewards based on their error magnitude when responding at specific ports. Remarkably, all rats tested in the task showed performance above the chance level by consistently choosing the correct port corresponding to the magnitude of their timing error in each trial. This proportion of correct choices directly reflects their ability to monitor temporal errors, as the reward was contingent upon the error magnitude.

Although the results of Kononowicz's study (2022) are exciting, it is crucial to acknowledge certain limitations that need to be taken into account. One significant limitation of the study involves the potential influence of differential reinforcement on rat behavior. The rats were trained to associate specific responses with varying rewards based on the magnitude of their temporal errors. This introduces the possibility that their behavior may be driven by reward anticipation. It is plausible that the rats learned to anticipate specific rewards associated with different timing errors and adjusted their behavior accordingly. Consequently, the interpretation of their heightened expectation for a reward may be confounded by the potential impact of reward anticipation resulting from the differential reinforcement schedule. Another limitation of Kononowicz's (2022) study is the lack of error directionality judgments. While the rats demonstrated self-monitoring of temporal errors, the focus was on error magnitude rather than error direction. The study categorized errors as small or large without considering the specific direction of the errors. As a result, valuable insights into the rats' cognitive abilities related to error directionality were not addressed.

Both the study by Kononowicz et al. (2022) and this study aimed to investigate the presence of MEM abilities in non-human animals, specifically rats and mice, respectively. Althoughboth studies focused on temporal errors and the animals' ability to judge the magnitude of these errors, there were notable differences in the experimental designs and measurement techniques. In Kononowicz's study (2022), the focus was placed on characterizing errors made by rats into two distinct groups, namely "small" and "large" errors. These error categories were then associated with a varying number of rewards, providing a direct measure of the error magnitude. In contrast, our study sought to determine whether mice possessed an

awareness of their temporal productions and errors relative to the target duration. To assess this, we measured the mice's anticipatory nose-pokes into the hopper as an indicator of their expectation and confidence for the reward. By comparing and contrasting the methodologies, measurements, and findings of these studies, we gain a comprehensive understanding of the robustness and generalizability of metric error monitoring abilities in non-human animals.

One significant advantage of our study is the deliberate avoidance of differential reinforcement of the nose-poke rate. Unlike previous studies (e.g., Foote & Crystal, 2007; Kononowicz et al., 2022), this study's experimental setup was specifically designed to eliminate the potential influence of reward anticipation and response-reward associations on the observed behavior. In our study, we implemented a temporal task where mice were required to press a lever for a target duration or longer to receive a reward. Importantly, we did not differentially reinforce the nose-poke rate associated with lever pressing. Instead, we solely focused on rewarding the mice when they met the target duration criterion. This ensured that any changes in nose-poke rate were not driven by the anticipation of rewards based on response rates, but rather by the mice's confidence or self-assessment of meeting the task criterion.

Our study also significantly contributes to the existing body of research on cognition in non-human animals. Studies, such as those by Kirk et al, (2014), Kheifets et al, (2017), Templer et al, (2017) and Joo et al, (2021) have laid a foundation for understanding metacognition-like behavior in animals. Kirk et al. (2014) investigated metacognition-like behavior in rats through a lever-pressing task in a T-maze. They observed that rats continued to press the lever even when the immediate reward was removed, indicating their inclination to seek information about the

location of food in the maze. Notably, the rats displayed heightened interest in obtaining more information when the lever press provided additional cues, such as in a maze with multiple arms. However, the rats stopped seeking information when the food location became certain or predictable. This study demonstrated the rats' cognitive ability to adapt their behavior based on the level of uncertainty. Building upon these findings, Kheifets et al., (2017) found that rats and mice have the ability to differentiate between their own measurement error and external timing uncertainty. Through time reproduction tasks, they created conditions where the animals had to distinguish their internal timing mechanisms from external factors that could potentially disrupt their timing accuracy. Their distinct response patterns when faced with increased measurement error or external timing variability, suggest the presence of multiple independent clocks in timing mechanisms. In the study conducted by Templer et al., (2017), rats' ability to assess their own memory strength was explored. By introducing a decline option within a memory task, the researchers allowed rats to opt-out of specific memory tests. The results demonstrated that rats performed significantly better on tests they actively chose to take, indicating their ability to discern between remembering and forgetting. Additionally, Joo et al. (2021) investigated the relationship between memory retrieval, memory confidence, and memory-guided decisions in rats. Through a spatial memory task, the researchers examined how rats utilized memory confidence in their decision-making process. The rats were required to make temporal bets indicating their confidence in the accuracy of their memory, and the potential rewards were influenced by their choices. The study revealed that rats exhibited a higher tendency to bet more for correct choices, reflecting their confidence in their memory.

Collectively, these studies contribute to the understanding of metacognition in non-human animals. They emphasize the cognitive mechanisms that enable animals to seek information, assess memory strength, and make decisions based on confidence. We demonstrated that mice possess the ability to accurately judge the metric information of their errors. Specifically, we observed that mice exhibited more vigorous nose-poking behavior when their time productions were close to the target duration compared to significantly shorter time productions. This finding suggests that mice, like rats, have the cognitive capability to discern whether their temporal performance meets the task criterion for reward. By highlighting the mice's ability to monitor their timing errors and accurately judge their performance, our study goes beyond previous research and provides new insights into the heightened expectation for a reward of mice. The investigation of metacognition in animals is of significant importance as it sheds light on the cognitive capacities of different species and broadens our understanding of animal cognition. By expanding our knowledge of cognition in mice, our research adds to the growing body of evidence supporting the existence of these processes across various animal species.

5.3: Mice are near-optimal timers

The accurate and precise timing performance demonstrated by the mice in our study further supports the notion of near-optimal timing behavior shown by Gür et al., (2022). Researchers used a differential reinforcement of response duration (DRRD) task which required mice to sustain a lever press for a minimum amount of time to receive reinforcement. Gür et al., (2022) discovered that the response durations of mice exhibited a positive bias, meaning their response durations tended to be longer than the minimum requirement. This positive bias in response durations was influenced by the level of endogenous timing uncertainty. In other words, the mice's inherent uncertainty or variability in their timing contributed to the observed bias in their response durations. This finding suggests that mice adapt their response durations based on their own timing uncertainty, aiming to optimize their performance in time-based tasks.

The mice in our study exhibited high temporal accuracy, consistently producing lever presses that were near or surpassed the minimum requirement, regardless of what the requirement was. This indicates their ability to finely discriminate and time intervals in order to receive a reward. The animals displayed behavioral patterns suggesting that they adapt their mean responses on the basis of their timing uncertainty.

These findings hold substantial significance as they contribute to a growing body of evidence that supports the optimality of temporal decisions in mice, particularly when considering the influence of timing uncertainty. The optimality of temporal decisions refers to the notion that animals possess the ability to make adaptive choices and judgments in tasks that involve temporal processing. In other words, they exhibit a capacity to estimate and

integrate temporal information to make decisions that maximize the expected reward rate. The remarkable capacity of organisms to adapt their behavior near-optimally by extending their waiting times in response to the level of timing uncertainty is another indication that they possess the ability to monitor and evaluate the direction and magnitude of their timing errors (Akdoğan & Balcı, 2017). It is precisely this intriguing aspect that motivated the focus of the present study on the metric components of errors.

5.4: Limitations and Future Directions

5.4.1: Optogenetics

There are still several avenues for future research to explore in regard to metric error monitoring in mice. One potential direction for further investigation is the utilization of optogenetics to mimic negative dopaminergic reward prediction errors in mice. Optogenetics is a powerful technique that involves using light to control and manipulate the activity of specific neurons in the brain (Deisseroth et al., 2006). It combines the principles of optics and genetics to introduce light-sensitive proteins, called opsins, into targeted neurons. These opsins can be selectively activated or inhibited by specific wavelengths of light, allowing us to modulate the neuronal activity with precise control. By using an inhibitory opsin, such as halorhodopsin, we can selectively suppress the activity of dopaminergic neurons immediately following a correct response. By doing so, we can transiently inhibit the activity of dopaminergic neurons below their baseline rate, mimicking a negative dopamine reward prediction error. As a result, the mice are expected to perceive that they have made an error, despite their correct performance, leading to a reduction in nose-poking behavior in the food hopper. Conversely, if we employ channelrhodopsin as an activator, we can selectively stimulate dopaminergic neurons following incorrect responses, mimicking positive dopamine reward prediction error. As a result, the mice may perceive a trial as successful even when they performed the task incorrectly, potentially leading to an increase in nose-poking behavior in the food hopper as they anticipate a reward.

5.4.2: Additional behavioural tasks

Many of our daily actions rely largely on approximate quantity estimates such as time intervals, numerosities, and distances, and making decisions based on these quantitative estimates. It would also be worthwhile to investigate the generalizability of metric error monitoring across different behavioral contexts and cognitive domains, as there is more than just the direction and magnitude of our errors. For instance, in addition to the direction and magnitude of errors, error monitoring can encompass other dimensions such as error type, error context, error consequences, and the influence of feedback. Different types of errors, including underestimations and overestimations, can have distinct cognitive and neural correlates, highlighting the complexity of error monitoring processes. Moreover, errors occur within specific contexts and situations, which can influence their significance and implications. Factors such as task demands, environmental conditions, and personal goals can shape the interpretation and evaluation of errors, impacting subsequent decision-making processes. Expanding on this, considering the consequences of errors is crucial in error monitoring. Errors can have varying degrees of impact, ranging from minor inconveniences to significant setbacks. Evaluating the consequences of errors allows for appropriate adjustments or interventions to be implemented, aiming to enhance performance.

This could involve examining error monitoring abilities in other timing tasks or assessing whether mice exhibit similar error monitoring processes in non-temporal activities, such as spatial or numerical tasks used in previous studies (e.g., Kononowicz et al., 2019; Gür & Balcı, 2017; Duyan and Balcı, 2018; Gür et al., 2022). For instance, Duyan and Balcı (2018) showed that humans monitor not only the magnitude but also the direction of errors in their

numerosity estimations by estimating the number of dots on a screen and retrospectively judging their confidence levels and direction. Following, Yallak and Balci (2021) investigated accuracy in temporal, spatial, and numeric domains by using tasks to confirm that metric error monitoring ability is commonly governed across different magnitude domains.

In mice, studies (e.g., Berkay et al., 2016; Çavdaroğlu and Balcı, 2016; Gür et al. 2021; Gür et al., 2022) have investigated count-based decision-making and established that mice can acquire and use numerical knowledge to form and guide decisions. These investigations have provided valuable insights into the cognitive abilities of mice related to numerical processing and decision-making. By employing paradigms and methodologies used in these count-based decision-making studies and integrating them with our investigation of metric error monitoring, we can significantly expand our understanding of how mice perceive and process errors in a broader cognitive context. Exploring the metric information of error monitoring in mice, as we did in the present study, allows us to investigate the extent to which mice use and integrate temporal and numerical information in their cognitive processes. Such investigations in mice or other non-human animals would contribute to our understanding of the generality and specificity of metric error monitoring abilities. Such investigations not only expand our understanding of metric error monitoring in mice but also contribute to our broader understanding of the generality and specificity of error monitoring abilities across species.

5.4.3: Investigating individual differences

Additionally, it is worth exploring the role of individual differences in metric error monitoring abilities. Variability in error monitoring could arise from genetic factors, prior

learning experiences, age, or other sources. Investigating the factors that contribute to inter-individual differences in error monitoring performance would deepen our understanding of the underlying mechanisms and potentially reveal novel avenues for intervention or modulation.

For example, it is important to consider the potential impact of housing conditions on metric error monitoring abilities in mice. In our study, some mice were group-housed, while others were housed alone due to experimental and weight constraints. This discrepancy in housing conditions could introduce variations in the observed outcomes, as social interactions and environmental enrichment have been shown to influence cognitive and behavioral processes in rodents (Zidar et al., 2019). Therefore, it is essential to acknowledge that the housing condition of the mice may serve as a limitation in our study.

Another example, and possible limitation to our study was the age of our mice. This study specifically began testing mice that were 8 weeks of age, and all mice were the same age. However, age can be a crucial factor influencing cognitive abilities including error-monitoring processes. Thus, it is possible that the developmental stage of the mice could impact their error monitoring performance. Many studies (e.g., Gür et al., 2019, 2020) have shown a significant age difference in decision-making and error-monitoring abilities in humans and animals. For example, Gür et al. (2020) investigated how decision-making is altered in aged mice and showed that the accuracy of perceptual decisions of old mice was significantly lower than that of younger animals. Colino et al. (2017) examined how age impacts error processing while performing a continuous tracking task in humans. They tested two groups (young vs. old) in performing a motor tracking task identical to that employed by Krigolson and Holroyd (2006)

while EEG data were recorded. Researchers found that older adults made more tracking errors than younger adults and, further, that the amplitude of the ERN was reduced in older adults relative to young adults following motor errors. Taking these studies into account means the generalizability of our findings to mice of different ages should be considered with caution, and future studies may benefit from exploring error monitoring abilities across different developmental stages.

5.4.4: Investigating sex differences

Another extremely important avenue for future research is to explore potential sex differences in metric error monitoring abilities in mice. Although this study focused exclusively on male mice, considering both sexes would provide a more comprehensive understanding of the generalizability of our findings. Some previous research has indicated that male and female mice exhibit similar patterns of timing behavior (e.g. Buhusi et al., 2017), suggesting that timing processes and error monitoring behaviour may not differ substantially between the sexes. While overall timing abilities may be similar, there could be differences in how males and females monitor and respond to errors.

Hormone changes in female mice, characterized by fluctuations in estrogen and progesterone levels across the estrous cycle, have the potential to influence error monitoring processes. Estrogen and progesterone are known to exert significant effects on various cognitive functions, including attention, memory, and executive functions. These hormones interact with neural systems involved in error monitoring (e.g., Luine & Frankfurt, 2013; Koss & Frick, 2017),

such as the prefrontal cortex and the anterior cingulate cortex, which are implicated in cognitive control and error detection processes.

It is essential to acknowledge that the exclusion of female mice represents a significant limitation in my study. It is also important to note Kononowicz and colleagues (2022) only used male rats in their study, therefore no research has investigated female metric error monitoring in non-human animals.

5.4.5: Investigating disease models

Research (e.g., Doenyas et al., 2019, 2020) has shown that individuals with ASD have impairments in the brain regions associated with error processing and monitoring, and therefore ASD patients show altered error monitoring. In the same realm, research has also demonstrated dysfunctions in error monitoring in individuals with OCD. Studies conducted by Grützmann (2016), Carrasco et al. (2013), and Fitzgerald and Taylor (2015) have shed light on the altered error monitoring processes in OCD. These findings suggest that individuals with OCD exhibit abnormalities in the brain regions associated with error detection and correction.

Employing my same study on disease model mice, specifically mice showing OCD and ASD phenotypes could allow for a direct comparison in error monitoring abilities between wildtype mice and the disease models. By investigating these disorders side by side, we have the potential to identify shared and distinct features of error monitoring deficits in OCD and ASD. This comparative approach could provide valuable information about the specific cognitive processes or neural systems that are disrupted in each disorder, potentially leading to a better

understanding of their underlying mechanisms and informing targeted interventions or treatments.

Given the frequently observed alterations in error monitoring abilities among individuals with ASD, it is anticipated that performing the same task in ASD models would yield divergent outcomes. Although typically developing mice tend to demonstrate higher rates of nose-poking in trials where their temporal productions are close to the target duration, mice with ASD phenotype may show different patterns. It is hypothesized that mice with ASD phenotypes may display reduced rates of nose-poking compared to typically developed mice, even when their temporal production is close to the target. This indicates challenges in accurately judging the proximity of their temporal productions to the task criterion. This deviation indicates altered MEM abilities and diminished confidence in their temporal estimations.

Given the heightened error monitoring tendencies observed in individuals with OCD, it is anticipated that performing the same task in OCD models would also show results that differ from wild-type mice. While typically developing mice may tend to exhibit higher rates of nose-poking in trials where their temporal productions are close to the target duration, individuals with OCD may show different patterns. Due to the heightened error monitoring tendencies, mice with OCD phenotypes may be less confident in their temporal estimations and display reduced rates of nose-poking. This discrepancy in nose-poking rates may indicate difficulties in accurately assessing the closeness of their temporal productions to the task criterion, resulting in decreased confidence and a tendency towards more cautious behavior.

Conclusion

To investigate metric error monitoring in mice, we employed a lever-pressing task where the mice were trained to depress a lever for a target duration to receive a reward. Through our observations of the mice's nose-poking behavior following temporal production during the test trials, we found that the mice displayed a higher rate of nose-pokes when their temporal productions were in close proximity to the target duration, indicating a heightened expectation for a reward. This evidence strongly supports the existence of metric error monitoring abilities in mice, highlighting their capacity to evaluate and monitor their own temporal productions.

Before our findings, studies had only shown MEM in humans and rats. By successfully demonstrating MEM abilities in mice, our study adds a novel and important contribution to the existing literature. The findings of this study have important implications for our understanding of animal cognition across species. The ability of mice to monitor their own timing errors based on confidence-like measures implies a rudimentary form of self-awareness. This challenges the traditional view that these abilities are limited to humans and other primates. The behavioral tool developed in this study provides a foundation for future research on the neural basis of metric error monitoring in non-human animals. Further investigations utilizing correlational and manipulative methods can shed light on the underlying mechanisms and neural circuits involved in this process in mice.

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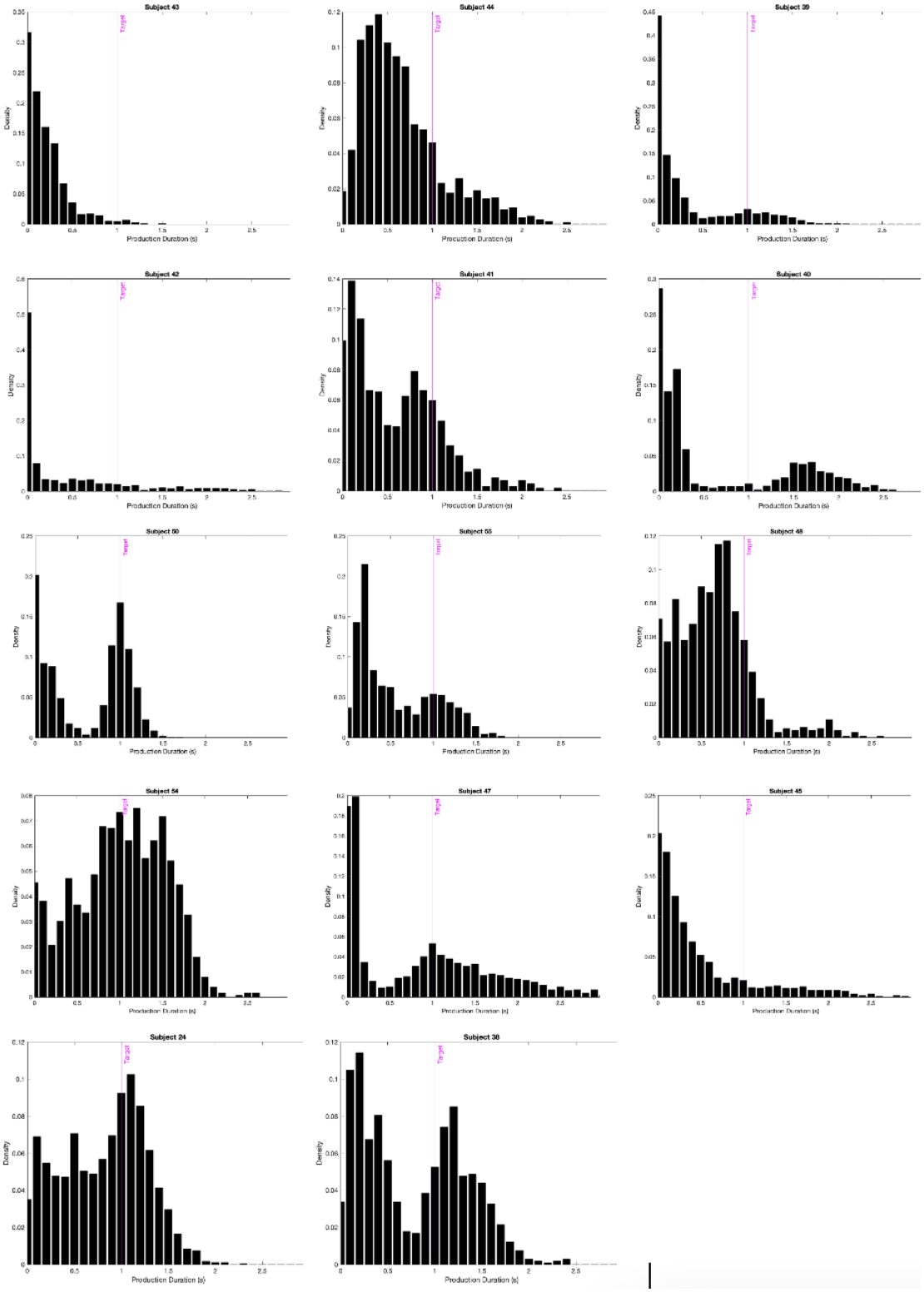
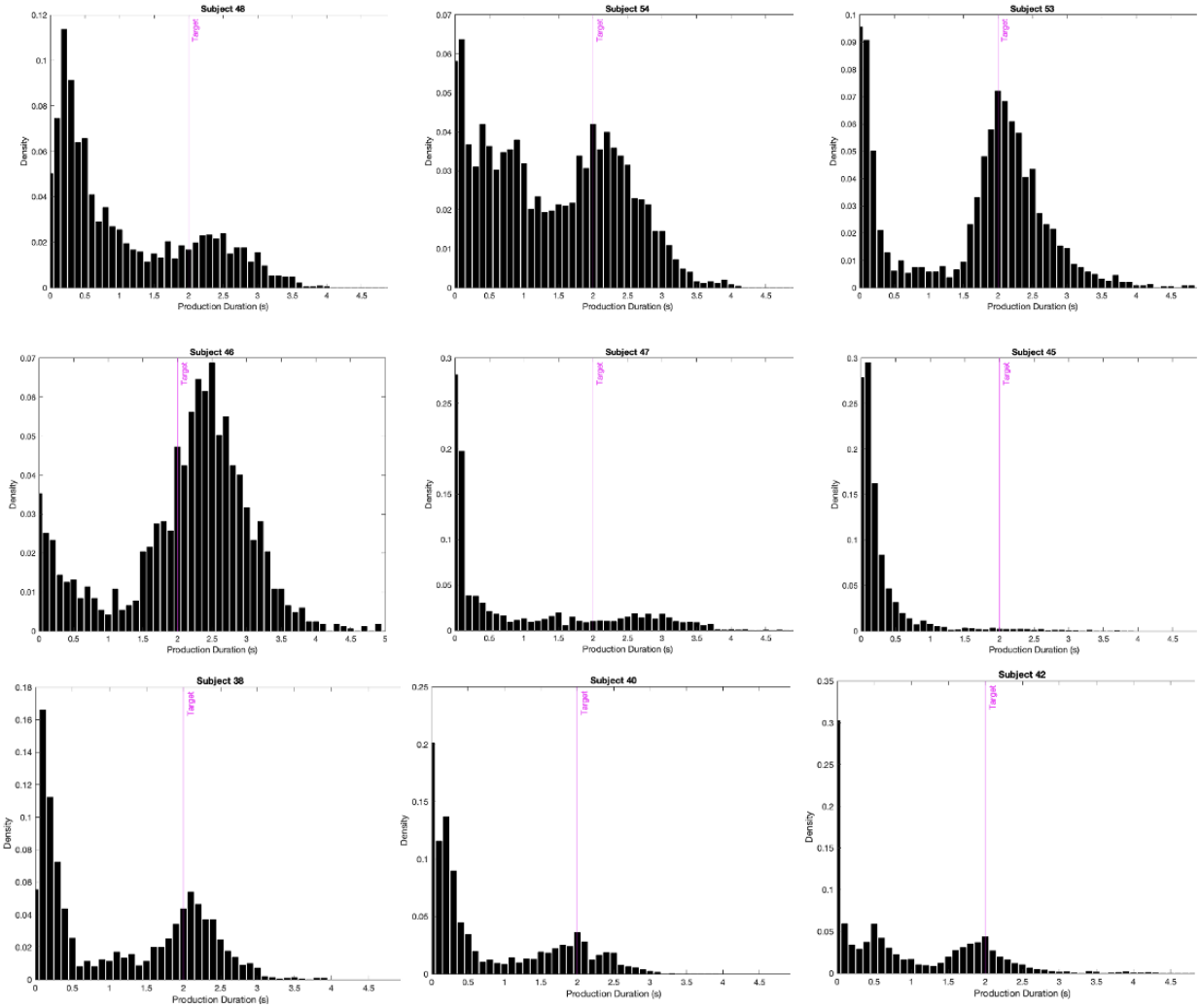
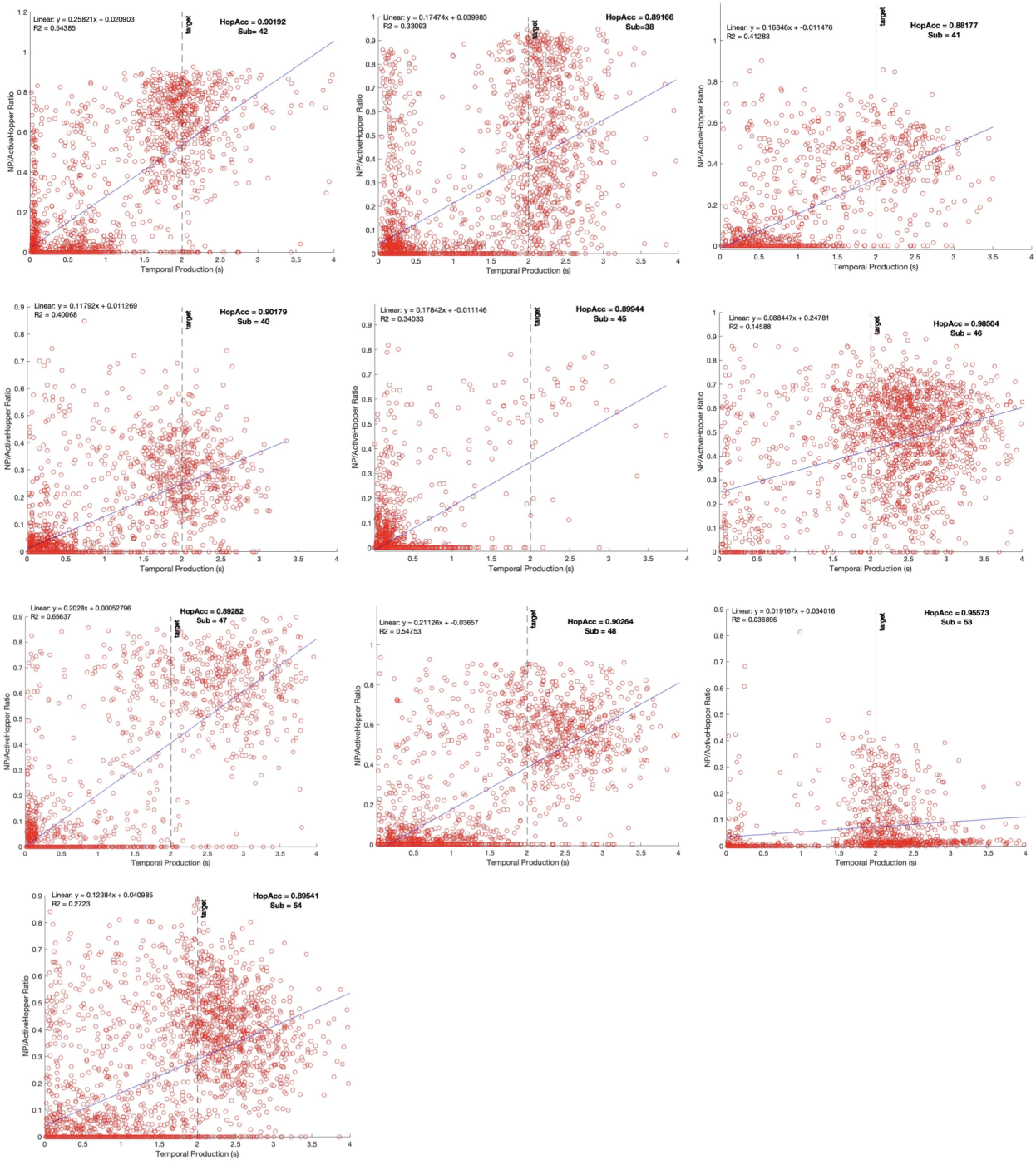
Supplementary Material



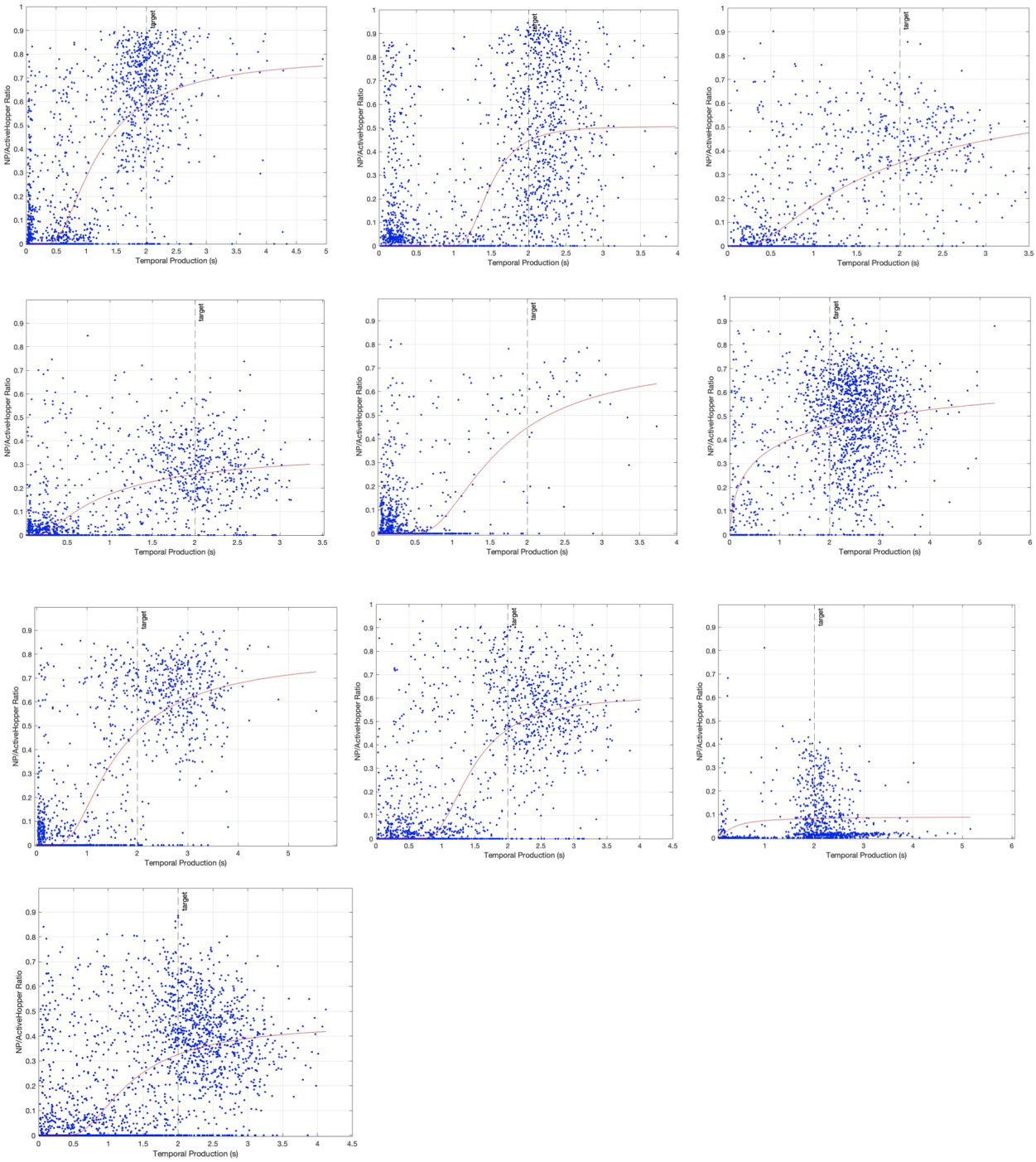
Supplementary Figure 1: Histogram plots illustrating the temporal production of mice for T = 1 second. Each plot represents an individual mouse and includes data from all testing sessions.



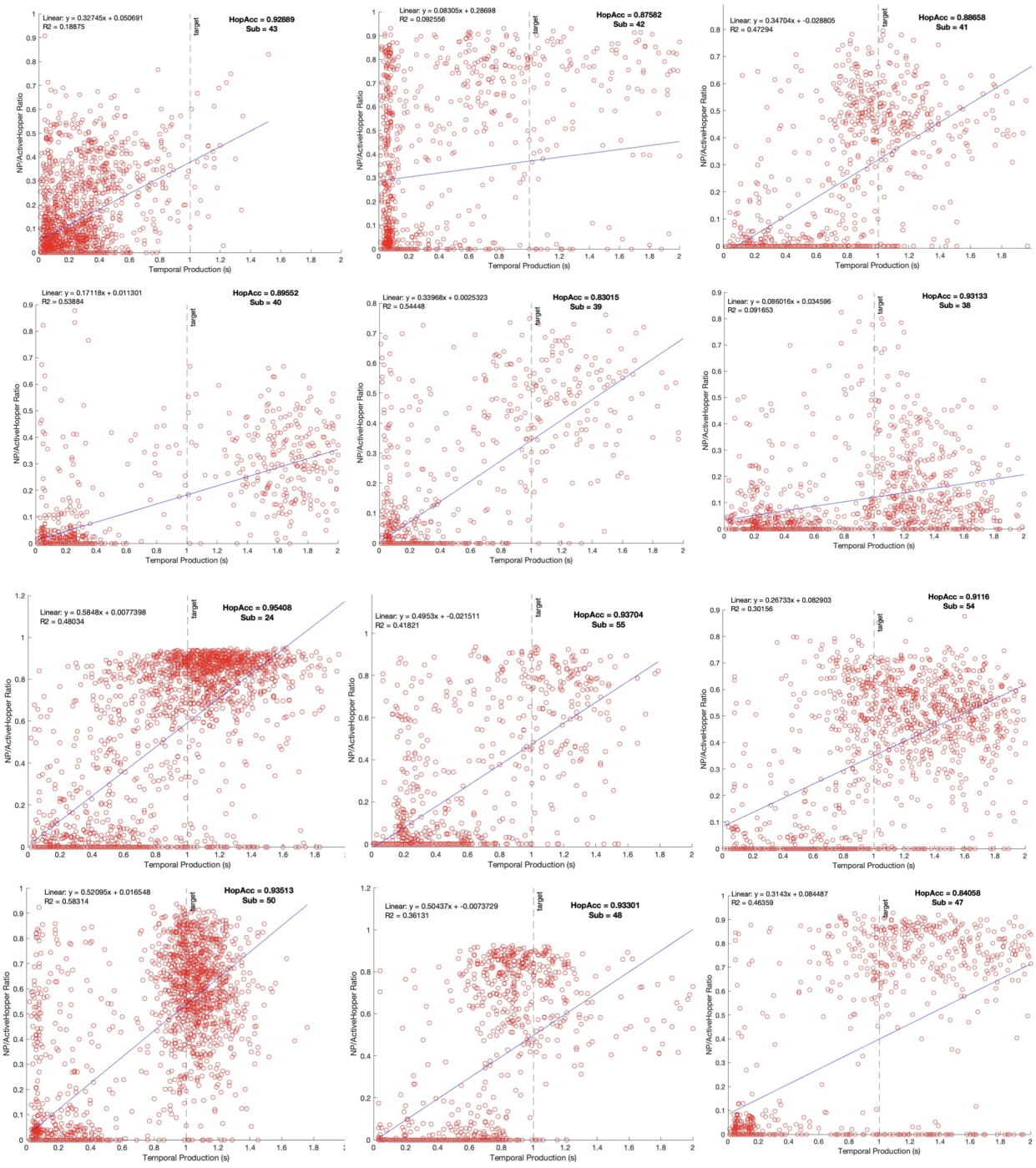
Supplementary Figure 2: Histogram plots illustrating the temporal production of mice for T = 2 seconds. Each plot represents an individual mouse and includes data from all testing sessions.

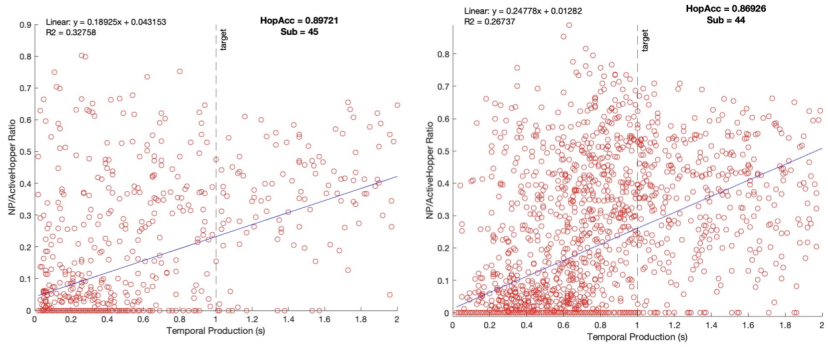


Supplementary Figure 3: Individual linear regression fits showing the relationship between nose-poke ratio and temporal production with target duration (T) = 2 seconds.

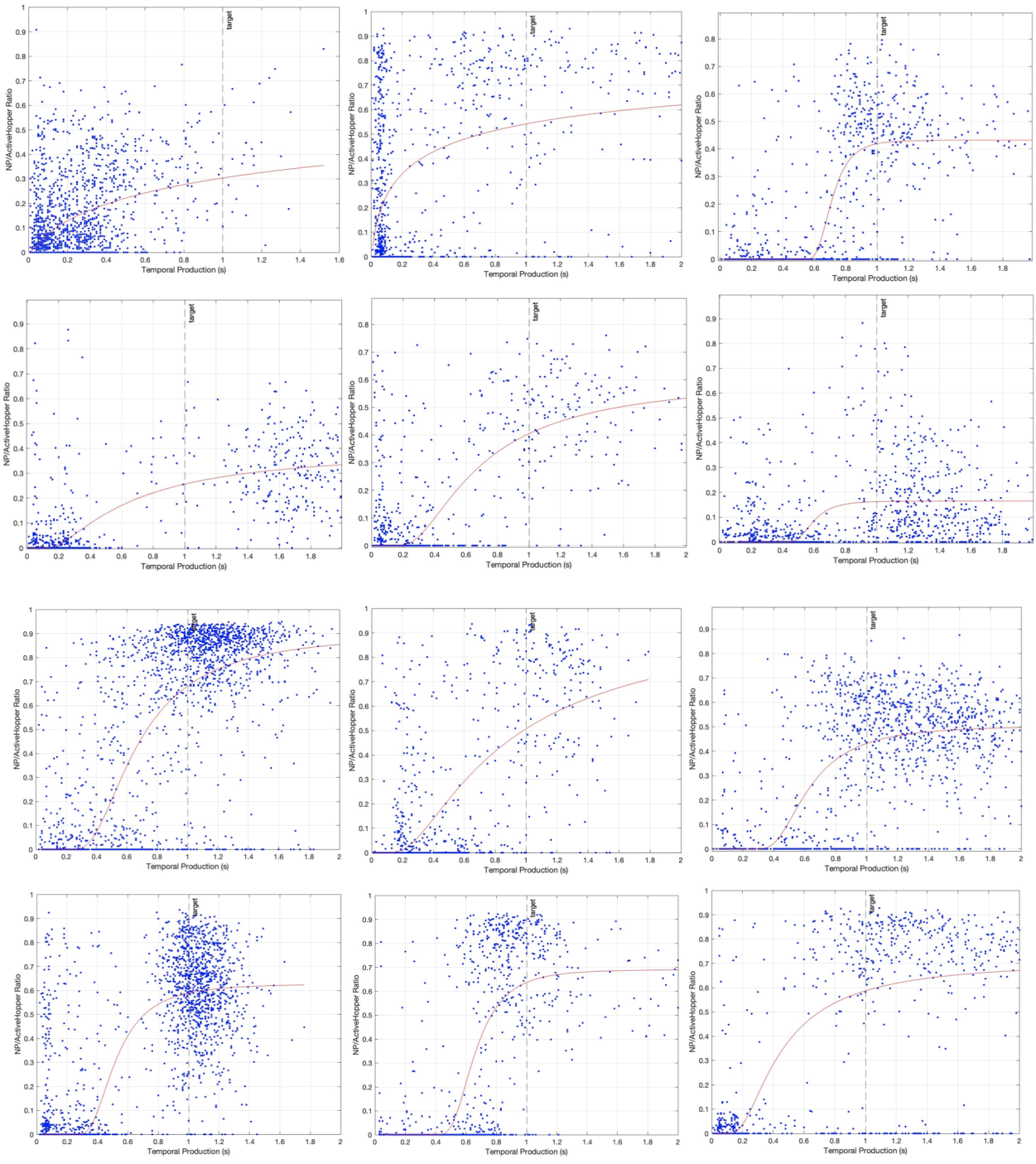


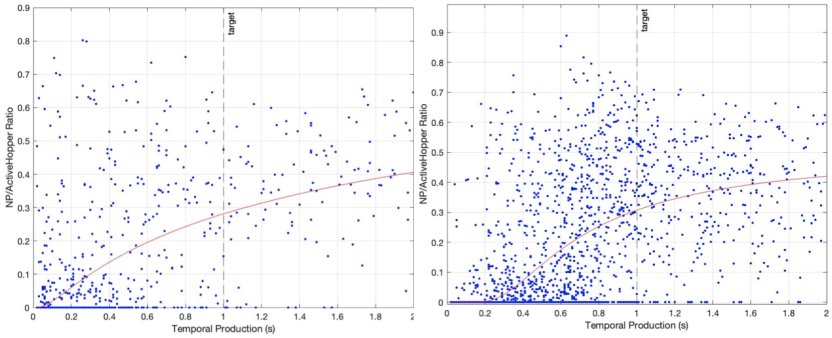
Supplementary Figure 4: Individual Weibull fits showing the relationship between nose-poke ratio and temporal production with target duration (T) = 2 seconds.


Linear: y = 0.32745x + 0.050691
R2 = 0.18875
HopAcc = 0.92889
Sub = 43
Linear: y = 0.08305x + 0.28698
R2 = 0.092556
HopAcc = 0.87582
Sub = 42
Linear: y = 0.34704x + -0.028805
R2 = 0.47294
HopAcc = 0.88658
Sub = 41
Linear: y = 0.17118x + 0.011301
R2 = 0.53884
HopAcc = 0.89552
Sub = 40
Linear: y = 0.33968x + 0.0025323
R2 = 0.54448
HopAcc = 0.83015
Sub = 39
Linear: y = 0.086016x + 0.034596
R2 = 0.091653
HopAcc = 0.93133
Sub = 38
Linear: y = 0.5848x + 0.0077398
R2 = 0.48034
HopAcc = 0.95408
Sub = 24
Linear: y = 0.4953x + -0.021511
R2 = 0.41821
HopAcc = 0.93704
Sub = 55
Linear: y = 0.26733x + 0.082903
R2 = 0.30156
HopAcc = 0.9116
Sub = 54
Linear: y = 0.52095x + 0.016548
R2 = 0.58314
HopAcc = 0.93513
Sub = 50
Linear: y = 0.50437x + -0.0073729
R2 = 0.36131
HopAcc = 0.93301
Sub = 48
Linear: y = 0.3143x + 0.084487
R2 = 0.46359
HopAcc = 0.84058
Sub = 47
target
NP/ActiveHopper Ratio
Temporal Production (s)



Supplementary Figure 5: Individual linear regression fits showing the relationship between nose poke ratio and temporal production with target duration (T) = 1 second.


target
NP/ActiveHopper Ratio
Temporal Production (s)



Supplementary figure 6: Individual Weibull fits showing the relationship between nose-poke ratio and temporal production with target duration (T) = 1 second.