Title of Thesis

Study on neural mechanisms of temporal expectation on a millisecond to second time scale

2019, March

Zhihan Xu

The Graduate School of

Natural Science and Technology

(Doctor's Course)

OKAYAMA UNIVERSITY

Abstract

Temporal expectation is the ability to focus attention to a future moment in time in order to reduce uncertainty about future events and optimize performance, which is fundamental survival skill to our life. In our daily environment, different sources can provide the relevant temporal information for us to generate temporal expectations, such as the regular rhythms (rhythmic expectations), symbolic cues (temporal orienting), and the probabilistic information associated with the passage of time (foreperiod effects). However, the neural mechanisms underlying these temporal expectations is not completely clear. Moreover, the distinction and relationship between different forms of temporal expectations is also unknown. Therefore, the aim of the present study was to clarify how our brain processes different types temporal information, and whether the processes will change with time scale.

First, to clarify whether different neural mechanisms exist in the temporal expectation driven by fast and slow rhythm. Direct comparison of fast rhythm manipulated according to a brief 500 ms inter-stimulus interval (ISI), and slow rhythm with a long 1700ms ISI, showed significantly greater activity of left middle frontal gyrus (MFG) and right insula, when temporal expectation driven by fast rhythm, but bilateral middle temporal gyrus (MTG), Superior frontal gyrus (SFG), left inferior temporal gyrus (ITG), and right caudate were more active when temporal expectation driven by slow rhythm. Revealed distinct neural mechanisms of fast and slow rhythmic temporal expectations.

Secondly, to investigate the effect of ISI length on temporal expectancy profiles (TEPs) for rhythm-based temporal expectation. A rhythm-based temporal expectation task with three lengths of ISI (500 ms, 1500 ms, 2500 ms) was conducted to examine the TEPs in the rhythmic temporal information processing. The results observed U-shaped TEPs with the reaction time decreasing to a minimum value at the expected moment before subsequently increasing again, and these TEPs were asymmetrical during millisecond time range, indicating that although regular rhythm priority generated a temporal expectation effect, the temporal expectations can be further updated by the passage of time, known as the hazard function. Additionally, the asymmetry gradually diminished as ISI increased, which suggested that, the effect of hazard function seemed to be attenuated with increasing ISI, when the participants perceive the target appear as unlikely as time passed, they disengaged their attention and tend to relax their preparation for the later foreperiod.

Thirdly, to further clarify whether temporal expectations driven by rhythmic cues differ from that driven by symbolic cues across millisecond and second timescales, we directly compared rhythmic and symbolic cued temporal expectation by means of a single experiment design. The results showed larger cueing effects for the rhythmic compared with symbolic cues. However, such difference was diminished as the time interval increased. The current study suggests that the distinction between the two forms of temporal expectation only exists in limited time range, as increased timescales, the mechanisms underlying the temporal expectations driven by rhythmic and symbolic cues likely to approach similar.

Lastly, just as we observed asymmetric TEPs in the second and third studies, supposed that although rhythm or symbolic cues priority generated a temporal expectation effect, the temporal expectation can be further updated by the passage of time. To further clarify how these temporal informations related to each other, the event-related potential (ERP) was performed to investigate whether temporal expectation driven by symbolic cues and the passage of time can work in parallel and have

distinguishable neural signature. Electrophysiological results showed evidence of two dissociable temporal expectation processes, as the two forms of temporal expectation seem to affect different stages of stimulus processing, a linear foreperiod effect was observed affect processing earlier than the expectation based on symbolic cues with a U-shaped pattern. Particularly, the current study provides the first evidence that temporal expectation driven by symbolic cues and passage of time can work in parallel with distinguishable neural signatures.

According to the current studies that examined the neural mechanisms underlying three kinds of temporal expectation across millisecond to second time scale limited to young adults, future studies will focus on development trajectory of temporal expectation across the life span to uncover the neural mechanism underlying different types of temporal expectations. Additionally, another important challenge is to extent to special populations (e.g. patients with Mild cognitive impairment, and Alzheimer's disease) to provide important basis for the early clinical detection and rehabilitation of special brain disease.

Table of Contents

Chapter 1 Introduction

1.1 Temporal expectation

Temporal expectation refers to the process of focusing resources on a specific moment in time in order to boost the responding to sensory events. The ability to generate temporal expectation is fundamental to our survival since it allows us to reduce uncertainty about the future and to optimize our performance. For example, crossing a busy street at the rush hour, deciding whether we should accelerate or have a break when our car arrives at an amber traffic light are just two among thousands of daily situations in which a uncorrect expectation may threaten our survival. Common experience informs us that directing attention on the predicted moment will lead to faster responses than if our mind is occupied elsewhere.

Temporal expectation is a rather broad concept, which contains multiple kinds of attention preparation in time. Temporal expectation can rely on different types of temporal information provided by the environment to prepare and respond at an optimal moment. Such as regular rhythms, symbolic cues and the passage of time.

1.1.1 Temporal expectation driven by the rhythm

When we perceive a rhythm, we are able to predict incoming event on the basis of the temporal structure given by the first few stimuli. Being exposed to a temporally regular environment, repetitive isochronous sequence of stimuli, such as flashing of a turning signal, ticking of a clock, we will expect the pattern to be continue and may thus expect the next flashing of the light or the next tick of the clock. When participants experience a temporal rhythmic and regularity of a sensory input, the participants themselves can spontaneously adapt behavior to the temporal structure. Therefore, the rhythmic temporal structure allows them to create a temporal template of the repeated non-random interval, which can be used to anticipate the likely moment for the next event occur.

Rhythmic contexts have been related to entrainment model. Attending is assumed as inherently oscillatory, anticipatory attending involves an engagement of internal oscillatory periods with the time interval of an isochronous sequence, whereas reactive attending involves phase alignments at stimulus onsets [1-4]. Figure 1.1 shows an oscillator adjusting to these aspects of an isochronous rhythm and targeting an attentional pulse to future onsets. The pulse constitutes an attentional focus in time, with varies in location and width as a function of temporal regularities; its location realizes an expectancy for a point in time, its width realizes a concentration of attending energy around that point. As shown, a wider attentional focus corresponds to a flatter expectancy profile, leading to a lower accuracy in judging temporal expected stimulus within the focus. In contrast, a narrower attentional focus corresponds to a shaper expectancy profile, which leads to a more precise attentional targeting in time and higher accuracy at rhythmically expected stimuli. This model implies that temporal expectancies can be stimulus-driven.

Performance accuracy was better when the target was presented in phase compared to out of phase with the preceding rhythm [5-7]. Similarly, response times have also been found to be improved when the stimuli appearing at the expected moment compared to an asynchronous rhythm using both auditory and visual stimuli [8-14]. Several neural correlates ware revealed by the electrophysiological measurements of brain activity for temporal expectations driven by rhythmic contexts. In post-target activity, when the target occurred at the expected moment, it was found the modulation of several ERPs related to both early sensory processing (attenuated N1 component) and late stimulus evaluation (enhanced N2 component and earlier P3 component) [9, 15].

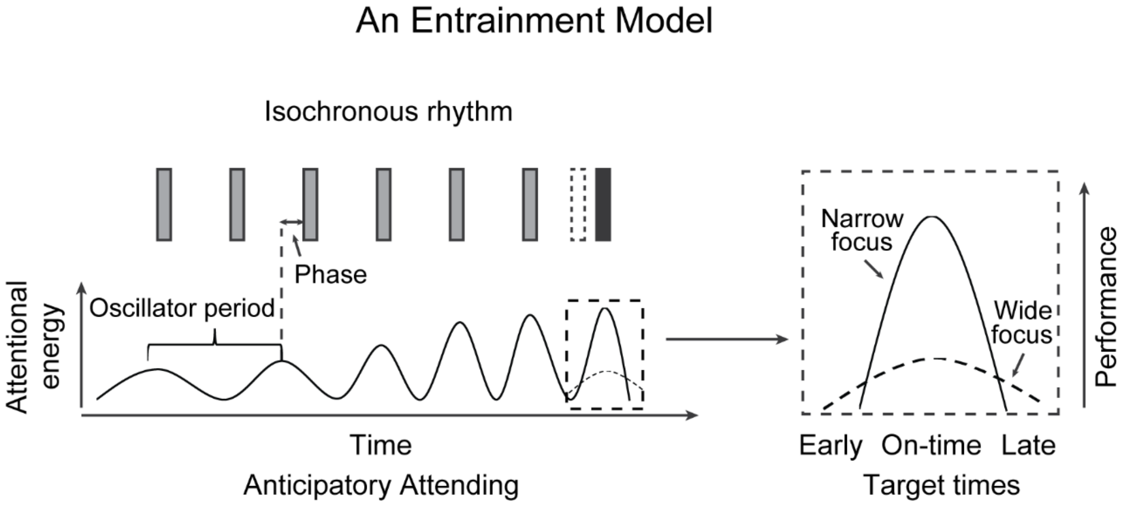


Figure 1.1. Schematic of entrainment model. Attending oscillator driven by an isochronous rhythm with fixed onset-to onset time interval between stimuli. Both the period and the phase of an internal oscillator adjust to the synchronize with successive stimulus onsets. The insert illustrates two attentional focus (pulse) widths: narrow (solid lines) and wide (dashes lines). Attentional energy is greatest at on-time expected moment.

1.1.2 Temporal expectation driven by the symbolic cues.

When predictive temporal information about when an event onset is given to participants by symbolic cues, based on learned temporal associations, which can be used to direct attention toward particular point in time, respond at the optimal expected time. For example, when a traffic light turns to amber, we can use the amber light predict when it is likely to turns red, allowing us to adjust driving behaviour, whether to brake or race through. In this situation, Color acts as an informative symbolic cue. This daily scenario can be defined as temporal orienting effect.

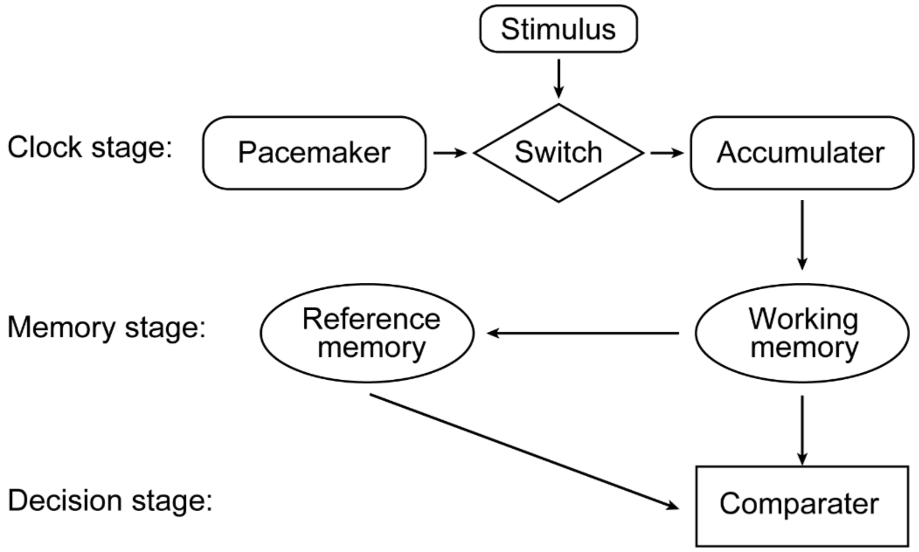


Figure 1.2. Schematic of interval model with clock, memory and decision stage. The clock stage involves a pacemaker emits continuous stream of pulses; stimulus trigger the closing and opening of a switch let the pulses gates in to an accumulator. The number of pulses switch serves as a duration code maintained in the working memory and transferred to a reference memory. Then, a comparison between the current code and a remembered standard code decide the response.

Temporal expectation driven by the symbolic cue have been related to interval model composed three-process stage (see Figure 1.2). During the clock stage, at the onset of a to-be timed event, a neural pacemaker emits a continuous stream of pulses. Stimulus trigger the closing of the switch allowing pulses gated into an accumulator marking the beginning of a time interval; Stimulus trigger the switch open making the ending of a time interval. Then, the number or count of the pulses between closing and opening switch, gated into the accumulator of serves as a duration code of the interval. During the next memory stage, the code of the duration for each interval are maintained in the working memory, then transferred to a more permanent reference memory. At last, at a decision stage, an updated comparison code is generated relative to a remembered standard code, when the current duration code reaches the temporal criterion, “time is up” and the currently timed interval is expected to end [16-20]. Thus, this processing reflected as enhanced performance (higher accuracy / faster reaction time) [21-23]. Neuropsychological research revealed that the mechanism of such temporal expectation, controlled, voluntary in nature, depends on the right frontal cortex [24].

1.1.3 Temporal expectation driven by the passage of time.

Even in the absence of temporal cues providing temporal information about upcoming events, temporal expectation can be deployed over time by flow of time itself. As time is experienced as a unidirectional dimension, the unidirectionality of “time’s arrow”, the passage of time itself carries predictive temporal information.

A classic example is the well-known variable foreperiod effect (FP). Foreperiod is the interval between a warning stimulus and an imperative stimulus (target). In order to illustrate, imaging waiting for a bus at station. The probability of the bus appearing as soon as you arrive at the bus stop is very low, but the probability of the bus appearance will increase as long as you wait for it. The longer you wait, the more your expectation grows. The phenomenon underlying such experience is known as the hazard function, which defined as the increasing conditional probability over time that an event will appear, given that it has not already appeared [25-27].

When foreperiod with different duration randomly presented trial by trial with the same a prior probability of appearance, the reaction time for target decreased with increasing foreperiods [25, 28-30]. The foreperiod effect has been mainly explained conditionally and intrinsically biases target predictability [27, 31-34]. The deficit in the temporal expectation driven by passage of time has been related to either left and right frontal lesion [24, 35, 36]. Transcranial Magnetic Stimulation, fMRI data further indicate that right lateral prefrontal cortex is integral in harnessing the temporal expectation driven by passage of time in order to improve performance [23, 37-39]

1.2 Related studies on temporal expectation

Different sources of temporal information can be used to predict the likely moment of the upcoming event onset, so as to optimize perceptual and motor performance [5, 25, 40, 41], such as regular rhythm, symbolic cues and the passage of time. However, the interrelationship between different forms of temporal expectations still under debated.

Rhythmic temporal expectation has been dissociated from symbolic cued temporal expectation in behavioural and electrophysiological studies [21, 22, 42, 43], as well as in neuropsychological studies, where rhythmic temporal expectation was not impaired after frontal lesion [24, 36, 44]. Rhythmic expectations has been suggest involved automatic temporal expectations, as the rhythm can generate temporal expectation in a bottom-up manner [5, 43]. Symbolic cued temporal expectation has been suggest involved controlled temporal expectations [35]. However, rhythmic temporal expectation also has been suggested may require integration of both automatic and controlled processes [45]. Thus, whether distinct mechanisms underlying temporal expectation driven by rhythm and symbolic cues still unclear.

Temporal expectation driven by symbolic cues and passage of time have been related to the proper functioning of frontal structures, suggested these two forms of temporal expectation rely on more evolved mechanisms, controlled and voluntary in nature, and based on top-down processing of time information [22]. Whereas, also other studies suggested distinguished pattern, as temporal expectations established by symbolic cues activated left inferior and superior parietal cortices, temporal expectation driven by the passage of time activated right inferior cortex. Thus, the relationship between temporal expectation driven by symbolic cues and passage of time has not been clearly established.

Differential effects of various drugs on millisecond vs second range timing have supported that millisecond vs second range timing are distinct processes [46], which can be differentiated not only physiologically [47] neuroanatomically [48] and also pharmacologically. Therefore, whether the neural mechanisms underlying these temporal expectations, and the relationship between them will change with timescales still unclear.

1.3 Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging or functional MRI (fMRI) measures brain activity by detecting changes associated with blood flow. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region also increases. One drawback with fMRI is the temporal resolution. As it takes several seconds for the blood flow to change, and the actual recording is limited by computational factors, the data collection is slowed down.

1.4 Event-related potentials (ERPs)

Event-related brain potentials are scalp voltage fluctuations resulting from electrical activity of cortical neural populations involved in the processing of sensory, cognitive or motor events. Which is non-invasive method of measuring brain activity during cognitive processing. Given their high temporal resolution, are useful for tracking ongoing cognitive processes. The transient electric potential shifts (so-called ERP components) are time-locked to the stimulus onset with the present trigger to marking the onset time. Each component reflects brain activation associated with one or more mental operations. Contrasting with behavioral measures such as response times, ERPs are characterized by simultaneous multi-dimensional online measures of polarity (negative or positive potentials), amplitude, latency, and scalp distribution. Therefore, ERPs can be used to identify and distinguish neural and psychological sub-processes involved in perceptual, motor, or cognitive tasks.

1.5 The purpose of the present dissertation

The main aim of this present thesis was to clarify how our brain processing different types temporal information, whether the processes will change with increased time scale. Moreover, whether distinct mechanisms underlying exist in temporal expectation driven by regular rhythms and symbolic cues, and whether temporal expectation driven by symbolic cues and the passage of time can work in parallel and have distinguishable neural signatures.

1.6 The contents of the dissertation

In chapter 1, the concept, related previous studies on three forms of temporal expectations on a millisecond to second time scale, and the theory of functional magnetic resonance imaging (fMRI) and event-related potential (ERP) were introduced. Meanwhile, the purpose and contents of this thesis were briefly described.

In chapter 2, we examined how the brain processing rhythmic temporal information by fMRI, and further investigated the different neural mechanisms underlying temporal expectation driven by fast and slow rhythm according to a brief or longer inter-stimulus interval (ISI).

In chapter 3, whether U-shaped temporal expectancy profiles (TEPs) existed in rhythm-based temporal expectation were examined, and the effect of ISI length on TEPs was further evaluated.

In chapter 4, we investigated the different behavioural benefit between temporal expectation driven by rhythmic and symbolic cues, by directly compared the two forms of temporal expectations by means of a single design. Furthermore, we assessed whether the distinction between the two forms of temporal expectation change with time scale.

In chapter 5, how the brain processing temporal information provide by symbolic cues and passage of time were examined by ERP, and whether the two forms of temporal expectation can work in parallel and have distinguishable neural signatures were further investigated.

In chapter 6, general conclusion based on the four experiments and the future challenges were presented.

Chapter 2 Different neural mechanisms underlying temporal expectation driven by fast and slow rhythm.

Summary

Timing can be referred to not only how long an event lasts (duration estimation) but also when an event occurs (temporal expectation). Several neuroimaging studies have proposed two dissociable mechanisms for estimation brief and loner interval durations. However, whether different neural mechanisms exist in the temporal expectation driven by fast and slow rhythm, still unclear. Direct comparison of fast rhythm manipulated according to a brief 500 ms inter-stimulus interval (ISI), and slow rhythm with a long 1700ms ms ISI, revealed that significantly greater activity of left middle frontal gyrus (MFG) and right insula, when temporal expectation driven by fast rhythm, but bilateral middle temporal gyrus (MTG), Superior frontal gyrus (SFG) and the left inferior temporal gyrus (ITG), right caudate were more active when temporal expectation driven by slow rhythm. Therefore, this research suggested distinct neural substrates for fast and slow rhythm based temporal expectations.

2.1 Background

Temporal expectation is critical to our survival since it allows us to selectively orient our attention in time in order to reduce uncertainty about the future and to optimize our behaviour. Deciding whether to stop or to accelerate when our car arrives at an amber traffic light or crossing a busy street, are just two parts per thousand of daily situations in which a bad temporal prediction of the correct time will threaten our survival.

In the laboratory, as in the real-world "Timing" can be referred to not only when an event occurs but also how long an event last. From the online Merriam-Webster English dictionary, one of the two distinct definition for the word "timing" is "The ability to select the precise moment for doing something for optimum effect (temporal expectation)". Here, the critical arguments are when best to act. The other definition is "observation and recording (as by a stopwatch) of the elapsed time of an act, action, or process". Here, the critical arguments are how long an event lasts (duration estimation).

Distinct Timing Hypothesis has been supported by several studies for discrimination of extremely brief and longer interval, which two dissociable mechanisms were proposed for the durations estimation in the sub-second and second time range, respectively [49]. The first study proposed this hypothesis assumed that durations less than approximately 300ms can be directly perceived, whereas longer durations need higher mental processes (Münsterberg 1889). Similarly, Michon (1985) suggested that temporal processing of brief intervals shorter than approximately 500ms is "of a fast, highly perceptual nature and not accessible to cognitive control", whereas for longer intervals is cognitively mediated [50]. Several studies employing a temporal discrimination task suggested that temporal processing of extremely brief intervals can be regarded as sensory-automatic system in nature and beyond cognitive control, while temporal processing of longer intervals demands higher-order cognitive system [51, 52]. Moreover, different brain areas have been suggested linked with the ability to estimate brief and long intervals. The bilateral anterior cerebellum was connected with brief interval, the right IPL was linked with longer duration estimation, in line with the idea that the capacity of attention and working memory support temporal discrimination in supra-second range [53]. However, whether different neural mechanisms exist in the temporal expectation driven by fast and slow rhythm, still unclear. Thus, in the current study, we compared fast rhythm manipulated according to a brief 500 ms inter-stimulus interval (ISI), and slow rhythm with a long 1700ms ms ISI, to investigate the neural mechanisms underlying fast and slow rhythm processing in temporal expectation.

2.2 Methods

2.2.1 Participants

20 healthy right-handed students participated in the behavioral experiment (15 males, 5 females; aged 21-29 years). Twenty healthy right-handed male participants took part in the fMRI experiment (aged 21-26 years). As the problems of our fMRI equipment, we failed of obtain all the behavioral data, for solving this, we added 20 participants for doing the behavioral experiment again. Because our fMRI data was analyzed by random effects model, our results have the generalization. All the participants with normal vision and none of them had a history of neurological or psychiatric dysfunction. The study was approved by the local research ethics committee in accordance with the declaration of Helsinki, and all participants gave their written informed consent.

2.2.2 Stimuli

Visual stimuli were generated on a personal computer and presented to the participants via a custom-built magnet-compatible video system during MR scanning. Stimuli were presented from Presentation 0.61. The stimulus was a circle designed as a dial with a hand located at the 12 o'clock position. Diameter of the circle was made with 15 degrees of angle of view from the centre of visual field with a fixation point of a cross. Constitute one stimulus, the hands at the 12 o'clock position turned to wider for 100ms, and then returned to quondam width for 100ms, the presentation time from first change of width to 5th lasts 900ms (5 times on and 4 times off), formed a flashing stimulus.

2.2.3 Procedure

A schematic of the tasks is showed in Figure 2.1. Started with the presentation of the flashing stimulus for 900ms (5 times wider and 4 times quondam). At the stimulus offset, the hand of the dial keeps still. Then, after a 500ms (fast) or a 1700ms (slow) inter-stimulus interval (ISI), the next stimulus starts to flash. Participants then made a speeded button press to the appearance of the flashing stimulus. They were told to make use of the temporal information carried by the ISI to predict when the stimulus starts to flash so as to respond to it as quickly as possible. A blocked design was used for the present experiment. In addition, tapping trial was designed as a baseline, in which participants just need to press the left and right button of the mouse alternately, when the word “task” appeared on the screen, then had a pause when a word “rest” appeared.

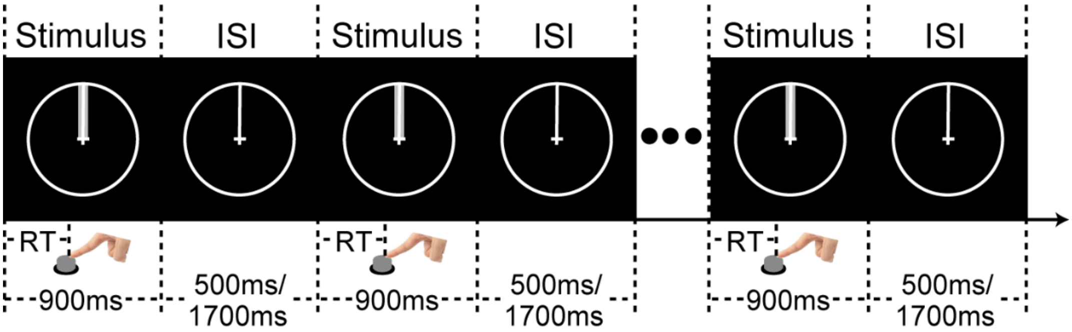


Figure 2.1 Schematic of the task. Flashing stimulus was presented for 900ms. Followed by 500ms or a 1700ms inter-stimulus interval (ISI), then the next stimulus starts to flash. Participants were instructed to respond to the onset of the stimulus as quickly as possible. Reaction time (RT) refers to the time between onset of flashing stimulus and the motor response.

2.2.4 fMRI scanning.

Images were acquired using a 3-T Siemens scanner vision whole-body MRI system to measure the brain activation with a head coil. The imaging area consisted of 32 functional gradient-echo planar imaging (EPI) axial slices (voxel size 3×3×4 mm, TR=4000 ms, TE=50 ms, FA=90°, 128×128 matrix) that were used to obtain T2*-weighted fMRI images in the axial plane. For each participant, we obtained 124 functional volumes.

2.2.5 Data Analysis

Behavioral data

Reaction time (RT) in the temporal expectation task refers to the time between onset of flashing stimulus and the motor respond. Then, we performed paired t tests to compare the fast (500ms) and slow (1700ms) rhythmic task.

fMRI data

SPM-Dicom import was used to convert the DICOM files to NIFTI files. The first four functional images were dumped because of the changeful contrast of image. Data preprocessing and statistical analyses were performed with the Statistical Parametric Mapping computer package (SPM8; Wellcome Department of Cognitive Neurology, London) implemented in MATLAB (The Math Works). All the volumes were spatially realigned to the first volume of the first-time series. There are sixteen participants whose movement parameters generated during spatial realignment less than 2mm. Realigned images were normalized using the standard EPI template in the Montreal Neurological Institute (MNI) reference brain coordinate space and re-sampled into 2×2×2mm voxels. Normalized images were smoothed by an isotropic 8 mm FWHM (full-width half maximum) Gaussian kernel.

Statistical analysis was performed into two stages of a mixed-effects model. In the first-level analysis, the BOLD response was modeled by a canonical hemodynamic response function (HRF) as the neural activity convolved with to yield regressors in a general linear model (GLM) for each condition. The time series in each voxel were high-pass filtered to remove low-frequency noise and then scaled within session to a grand mean of 128. AR (1) (first-order autoregressive) model, in which the temporal autocorrelation was estimated by pooling over suprathreshold voxels [15] was accommodated the Nonsphericity of the error covariance.

The sixteen subjects' contrast images of the first-level analysis were then used for the second-level group statistics. For identifying the whole brain activation for time expectations, ANOVA (one-way repeated measure analysis of variance) was used to examine average positive and negative activations of the 2 conditions when compared to each other. Only effects surviving an uncorrected threshold of $p < 0.005$ and including 50 or more contiguous voxels were interpreted for the average activation.

2.3 Results

2.3.1 Behavioral Data

Showed in Figure 2.2, mean RT for the fast rhythm was 253.8ms, for the slow rhythm was 269.3ms. The RT for fast rhythm seems faster than the slow rhythm condition. However, pair-wise comparisons of statistical analysis showed no significant difference.

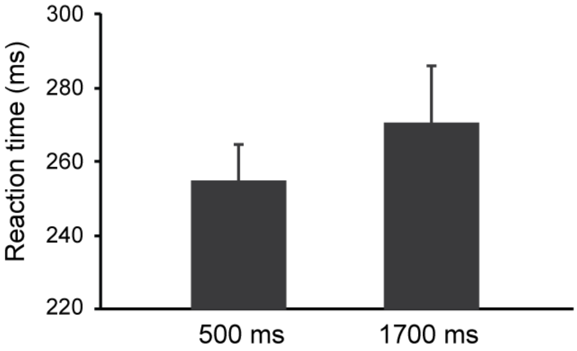


Figure 2.2. Mean RT for temporal expectation driven by fast and slow rhythm. Error bars represent the standard error of the mean.

Table 2.1. Brain regions differentially activated by the 500ms versus 1700ms ISI condition. Activations are significant at P<0.005 uncorrected.

Cluster Size (voxels)	Anatomy Region	Z score	x	y	z
220	Insula (R)	3.7	38	12	4
		2.6	32	12	14
101	Middle Frontal Gyrus (L)	3.3	-34	48	30
		3	-42	40	28

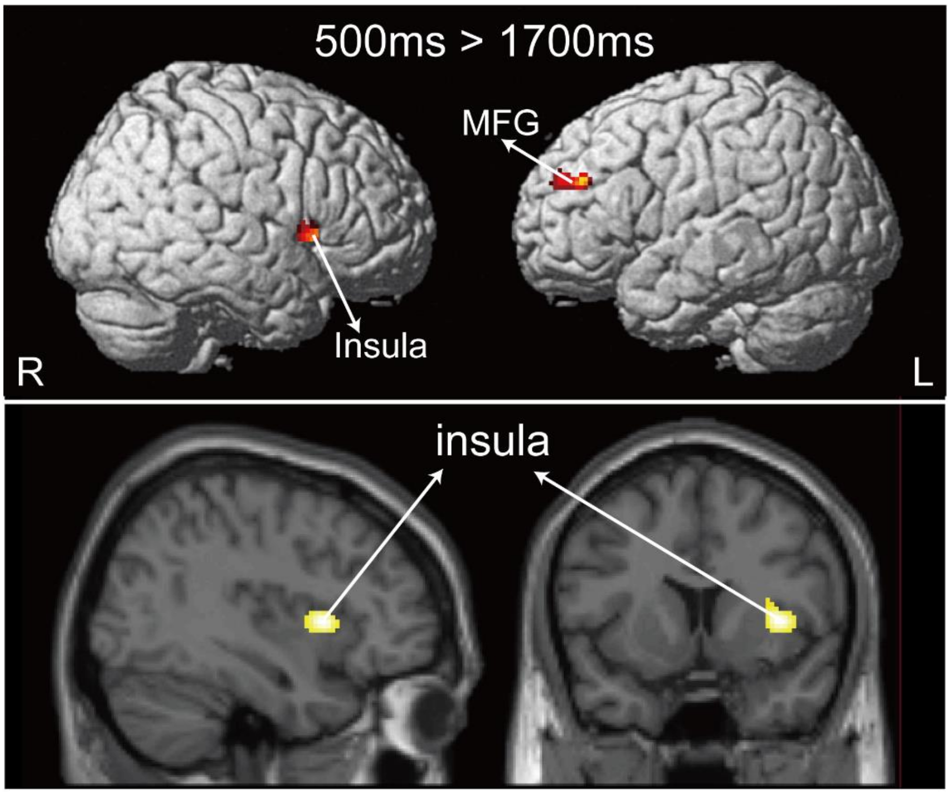


Figure 2.3. 500ms versus 1700ms ISI condition. Temporal expectation driven by fast rhythm with 500ms ISI preferentially activated several regions of right insula and left middle frontal gyrus (MFG). Effects are thresholded at P<0.005 (uncorrected).

2.3.2 fMRI Data

We first examined the activation which was better associated with the fast rhythm compared with the slow rhythm condition. To restrict this analysis to the regions constituting the temporal expectation network revealed by the comparison of the fast with the slow trials, we used this former condition as an inclusive mask. By comparing the ([500ms condition-1700ms condition] masked by [500ms condition]), significantly activated the right hemisphere Insula and left middle frontal gyrus (MFG) (Figure 2.3; Table2.1).

Table 2.2. Brain regions differentially activated by the 1700ms versus 500ms ISI condition. Activations are significant at P<0.005 uncorrected.

Cluster Size (voxels)	Anatomy Region	Z score	x	y	z
276	Superior Frontal Gyrus (R)	5.1	18	36	60
		3.2	24	22	66
257	Caudate (R)	4.3	18	-42	16
		3.4	22	-30	24
268	Superior Frontal Gyrus (L)	4.1	-28	26	60
		3.7	-4	36	62
58	Inferior Temporal Gyrus (L)	3.6	-56	-4	-16
		3.1	-50	-10	-22
182	Middle Temporal Gyrus (R)	3.5	50	-64	28
		3.1	48	-52	24
68	Middle Temporal Gyrus (L)	3.2	-44	-66	30
		2.9	-44	-72	36

Second, we examined the activation which was better associated with the slow rhythm compared with the fast rhythm. To restrict this analysis to the regions constituting the temporal expectation network revealed by the comparison of the slow with the fast trials, we used this former condition as an inclusive mask. By comparing the ([1700ms condition-500ms condition] masked by [1700ms condition]), significantly activated the bilateral middle temporal gyrus (MTG), Superior frontal gyrus (SFG), left inferior temporal gyrus (ITG) and right caudate (Figure 2.4; Table 2.2).

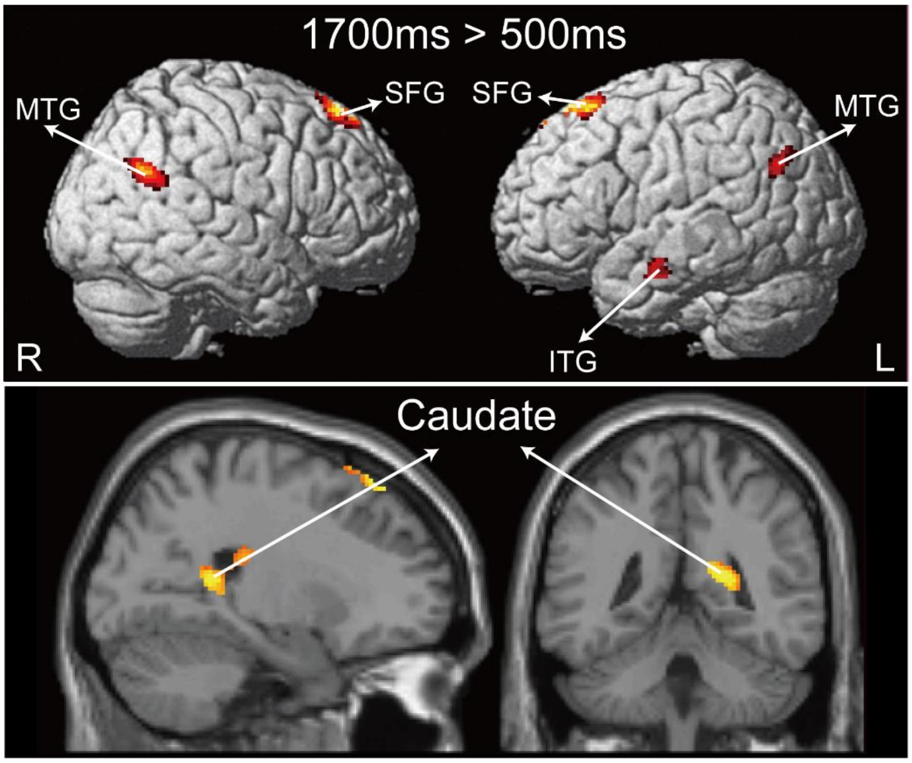


Figure 2.4. 1700ms versus 500ms ISI condition. Temporal expectation driven by slow rhythm with 1700ms ISI preferentially activated several regions of bilateral middle temporal gyrus (MTG), Superior frontal gyrus (SFG), left inferior temporal gyrus (ITG) and right caudate. Effects are thresholded at P<0.005 (uncorrected).

2.4 Discussion

The role of insula in the fast rhythm-based temporal expectation (Figure 2.3). Insula has been suggested to be the essential for time perception. Previous studies have shown activation in posterior and middle insula during the reproduction of time durations of visual and auditory stimuli, suggested the role of the insula in time perception [54, 55]. Note, however, that the use of time for implicit prediction (temporal expectation) and for the explicit estimation or reproduction of time intervals (time perception) does not necessarily involve the same functions and neural structures [56]. The engagement of the insula during fast rhythm-based temporal prediction is consistent with previous studies on time perception and extent the implying that the insula can also role in forming temporal expectation. Additionally, insula has also be suggested role in the time keeping [57]. As well known that successful temporal prediction requires accurate timekeeping (supported by temporal difference reward learning) as well as vigilance, attention and working memory. This finding supported the accumulation function of the insula, which assumes that our sense of time reflects the accumulation of physiological changes in body states.

Several neuroimaging studies demonstrated a network which is often known as the salience network (SN) consisting of the left anterior insula (lAI), right anterior insula (rAI) and dorsal anterior cingulate cortex (dACC) is activated in sensory stimulus-guided goal-directed behaviors. This network plays a crucial role in integrating sensory stimuli to implement and maintain task sets [58], to initiate cognitive control [59], and to coordinate behavioral responses [59]. Craig (2002) assumes that signals received in the dorsal posterior insula which is the primary sensory area for visceral, signals, are processed in a posterior-to-anterior progression and then cumulates in the anterior insula, which is associated with the visceral states and awareness of emotional. Thus, the insula was suggested sequentially integrates body states and internal autonomic responses with motivational and cognitive conditions, the former being instantiated by distributed neural processes across the brain. There are some studies showed the posterior insula to be a key neural substrate for the encoding of duration of multiple seconds [60]. It is remarkable that in the encoding phase of the task no explicit motor or other verbal response related to time is required. Only in the prediction phase a motor response has to be given, a stronger awareness of actual duration was potentially requiring, which is associated with anterior insula activation. Thus, the build-up of a representation of duration in the posterior insula during the encoding phase (not necessarily leading to an explicit account of time) is followed by activation of the anterior insula, inferior and medial frontal regions in the prediction phase where an explicit action is made.

The role of superior frontal gyrus (SFG) in the slow rhythm-based temporal expectation (Figure 2.4). SFG is thought to contribute to higher cognitive functions and particularly to working memory, which suggested by a study found that patients with a superior frontal gyrus lesion were globally impaired in working memory tasks. Taken in conjunction with the fact that the impairment was still present months to years after the removal of the lesioned area, indicated that the working memory is a key component of the working memory network [61]. In addition, the SFG was significantly associated with the down-regulation of both, arousal, and valence self-reports. This was confirmed by the regional VBM analysis, were right SFG regions showed significant positive correlations with reappraisal ability.

It was noteworthy that the caudate nucleus showed greater activation for the long than short inter-stimulus interval prediction. Evidence that the striatum is a likely candidate for sub serving time coding in temporal discrimination tasks has been provided by pharmacological and lesion studies in animals [62]. Neuropsychological studies in patients with Parkinson's disease [63, 64] also indicate that the striatum plays an important role in interval timing. Thus, they found that patients in these studies were impaired in their ability to estimate time intervals, who had decreased striatal functioning due to dopaminergic depletion. Moreover, Matell et al. 2003, using recordings of cortical and striatal ensembles in rats, suggested that the encoding of specific durations in neurons' firing rate, which may image the output of clock mechanisms. Our results, showing an additional activation in the caudate nucleus for the long inter-stimulus interval prediction, are in line with this assumption and support the same mechanism in humans.

2.5 Conclusion

Directly compared the temporal expectation driven by fast and slow rhythm in fMRI. We observed significantly greater activity of left middle frontal gyrus (MFG) and right insula, when temporal expectation driven by fast rhythm, but bilateral middle temporal gyrus (MTG), Superior frontal gyrus (SFG) and the left inferior temporal gyrus (ITG), right caudate were more active when temporal expectation driven by slow rhythm. Overall, this research revealed distinct neural substrates for temporal expectation driven by fast and slow rhythm.

Chapter 3 Effects of interstimulus interval length on temporal expectancy profile for rhythm-based temporal expectation.

Summary

Rhythms have been proposed to entrain the periodic fluctuations in attention to optimize perceptual processing. Previous studies have reported that time estimation accuracy declines systematically as the standard interval differs from the rhythmic context rate, creating an inverted U-shaped temporal expectancy profile (TEP) in explicit duration estimation tasks; however, evidence for TEPs are limited in implicit temporal expectation tasks. In addition, whether the length of the interstimulus interval (ISI) between each rhythmic stimulus affects rhythm-based temporal expectation processing remains unexplored. In the current study, we verified U-shaped TEPs for the rhythmic temporal expectation task. These TEPs were asymmetrical during the 500 ms and 1500 ms ISI and gradually became symmetrical during the 2500 ms ISI condition, indicating that although regular rhythm priority generated a temporal expectation effect, the temporal expectations can be further updated by the passage of time. Additionally, reaction times were progressively slower with increased ISI, which suggests that the rhythm perceived is limited; as the ISI increases, the rhythmic organization tends to collapse, resulting in less stable synchronization performance.

3.1 Background

Being exposed to a temporally regular environment, repetitive isochronous sequence, such as ticking of a clock, flashing of a turning signal, we will expect the pattern to be continue and may thus expect the next tick of the clock or the next flashing of the light.

When we perceive a rhythm, we are able to predict incoming event on the basis of the temporal structure given by the first few rhythmic stimuli.

Rhythmic contexts have been related to entrainment model. Attending is assumed as inherently oscillatory; anticipatory attending involves an engagement of internal oscillatory periods with the time interval of an isochronous sequence, whereas reactive attending involves phase alignments at stimulus onsets [1]. Several lines of research have reported that time estimation accuracy peaks when stimulus onset occurs at an expected point of time, declined systematically as a standard interval differed from a context rate, generating an inverted U-shaped temporal expectancy profile (TEP). Whereas, evidence for TEPs have only been proved exist in duration estimation tasks, but are limited in temporal expectation tasks [5, 41, 65].

Timing can be measured explicitly by duration estimate task, which elapsed time of sensory event or a motor act require to be registered and measured overtly [66, 67]. In the explicit task, participants are instructed they must learn a reference duration, then compare this duration with probe durations (shorter, equal or longer). Timing can also be measured implicitly by temporal expectation tasks, here, accurate timing facilitates the sensorimotor task goal, which is to process the event as quickly as possible [68]. In such condition, RT is the critical measure. Timing is required both for explicitly estimating the duration of a currently unfolding event, or implicitly predicting when a future event is likely to occur. Moreover, several studies have suggested a divergence in the way the two forms of temporal representation are ultimately translated into behaviour [69-71]. Additionally, the scalp distribution of implicit timing and explicit timing has also been proved neuroanatomically distinct [72-74], the results of functional neuroimaging studies further confirmed this neuroanatomical distinction, in which explicit timing activates right-lateralised fronto-striatal network [56, 75], implicit timing activates a predominantly left-sided inferior parietal cortex [40, 56, 76].

Therefore, it remains currently unclear whether the inverted U-shaped TEPs observed in explicit duration estimate task, can also exist for the implicit temporal expectation task. Moreover, as millisecond vs second range timing have been suggested distinct processes [67], which can be differentiated not only physiologically [47] neuroanatomically [48] and also pharmacologically. Thus, whether the length of interstimulus interval (ISI) between each rhythmic stimulus affect the rhythm-based temporal expectation processing, remains unexplored.

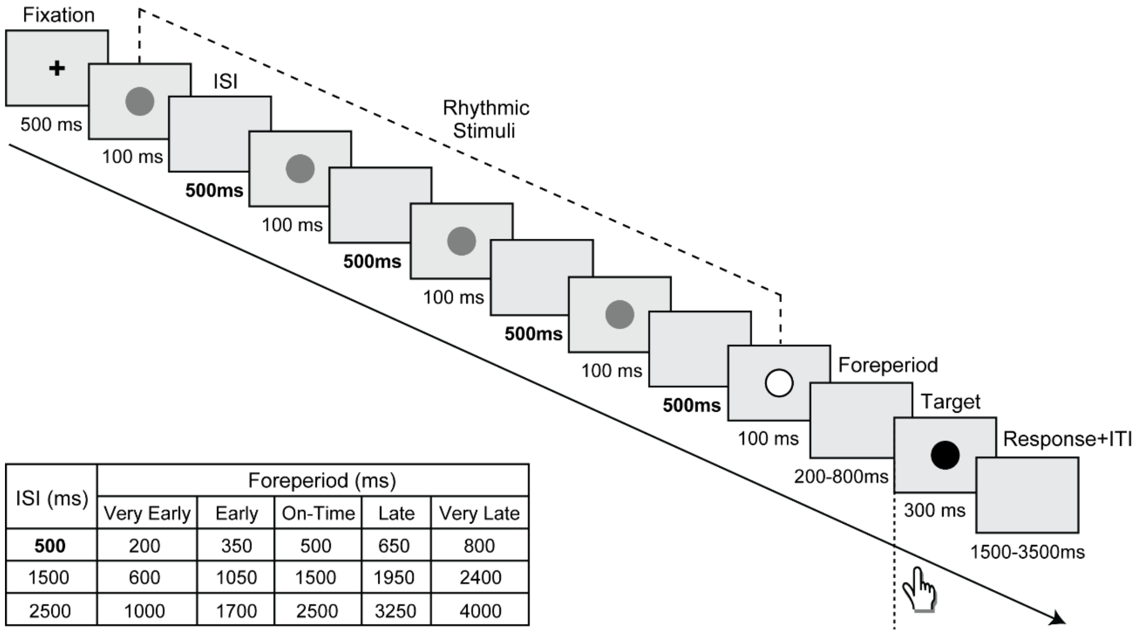
3.2 Methods

3.2.1 Participants

A total of 15 right-handed volunteer participants (14 males and 1 females) mean age of 23 years from the Okayama University participated in the study. All participants had no record of psychiatric disorders and had normal or corrected-to-normal vision. The study was approved by the institutional ethics committee, and all participants gave written informed consent before being enrolled.

3.2.2 Stimuli

We used Presentation 0.61 software to present stimulus and record behavioural data. Each trial included a fixation point, an isochronous sequence of rhythmic stimuli and a target, all the stimuli were presented at the centre of a 17-in monitor over a grey background (RGB=180,180,180), with a resolution of 1280*720 pixel. The fixation point was a black "+" symbol (0.6°× 0.6° of visual angle at a viewing distance of 90cm). The rhythmic stimulus was gray circle (diameter = 1.2°; RGB = 100,100,100), expect for the last one turned white (diameter = 1.2°) to warn about the impending target. The target was a black circle (diameter=1.2°).



ISI (ms)	Foreperiod (ms)				
	Very Early	Early	On-Time	Late	Very Late
500	200	350	500	650	800
1500	600	1050	1500	1950	2400
2500	1000	1700	2500	3250	4000

Figure 3.1. Each trail started with a fixation point, followed by rhythmic stimuli which consisted of five, six, or seven gray stimuli, each 100ms in duration, and presented with 500ms, 1500ms, or 2500ms inter-stimulus interval (ISI). The last rhythmic stimulus turned to white circle served as a warning signal, marked the beginning of the preparatory interval (foreperiod). A black circle target appeared for 300ms after a variable foreperiod followed the rhythmic stimuli, participants were instructed to respond as quickly as possible while avoiding anticipation by pressing the left button with their index fingers.

3.2.3 Procedure

Participants were seated comfortably in a quiet room, with their head fixed by a chin, about 90cm from the center of the monitor. A schematic of the tasks is showed in Figure 3.1. Each trial started with a fixation point for 500ms. Followed by an isochronous sequence consisted of 5/6/7 rhythmic gray circle stimuli appeared for 100ms and disappeared 500 ms, 1500 ms or 2500ms changed from trial to trial (depending on the ISI condition; see table in Figure 3.1). All the rhythmic stimuli were gray circle, expect the final one was a white circle act as a warning stimulus marked the beginning of the preparatory foreperiod (the interval between a warning stimulus and a target). The different number of rhythmic stimuli was designed to prevent the white circle being fully predictable. Following the rhythmic stimuli, a black circle target appeared for 300ms after a variable foreperiod (described below, also see the table in Figure 3.1), participants were instructed to respond as quickly as possible while avoiding anticipation by pressing the left button with their index fingers. A random inter-trial interval of 1500-3500 ms was included.

Table 3.1. Mean RT for each ISI (500 ms, 1500 ms, 2500 ms) and foreperiod (very early, early, expected, late, and very late).

	500 (ms)	1500 (ms)	2500 (ms)
Very early	333 (12)	376 (14)	374 (15)
Early	272 (11)	300 (10)	290 (10)
Expected	244 (8)	259 (9)	272 (9)
Late	263 (13)	268 (11)	308 (12)
Very late	274 (9)	331 (13)	407 (16)

Values in parentheses are standard errors of the mean.

3.2.4 Design

The participants completed a total of 240 trials. The target appeared after an expected foreperiod (500ms / 1500ms / 2500ms) in 60% of the trials, and the probability for the unexpected foreperiod was set to 20% of the trials, in which two foreperiod (very early and early foreperiod) were shorter than the expected foreperiod (0.4, 0.7 proportion of expected foreperiod), two foreperiod (late and very late foreperiod) were longer than the expected foreperiod (1.3, 1.6 proportion of the expected foreperiod). For example, for the 500ms ISI condition, the expected foreperiod was 500ms and the unexpected foreperiod were 200, 350, 650 and 800ms. In another 20% of total the trials the target was not presented (catch trials). In catch trials, there was no black circle target, but a gray background was displayed after the warning signal. The manipulation was included to prevent expectations to be generated based on conditional probability, thus help attenuate the effects of "hazard function", which is defined as the increasing conditional probability over time that a target is going to appear if it has not already appeared [32, 33, 77].

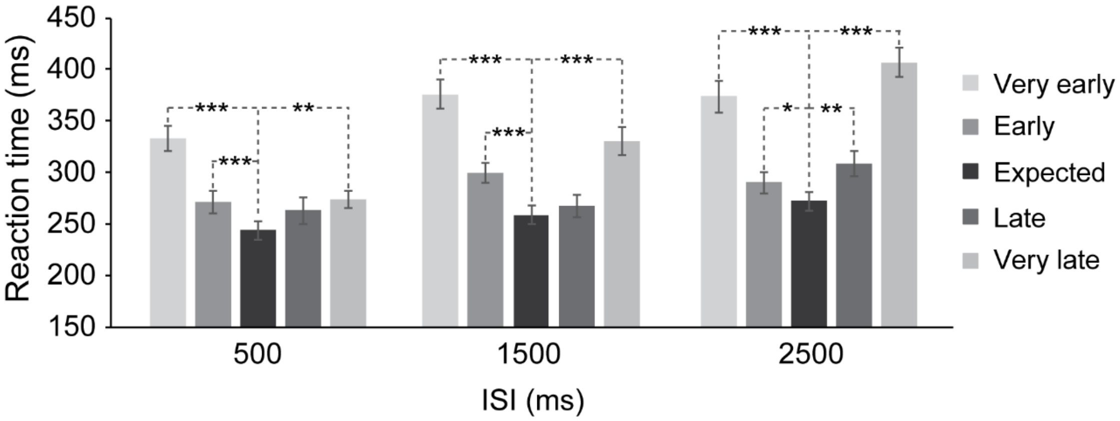


*Figure 3.2. Mean RT for each foreperiod during 500 ms and 1500 ms ISI conditions. Error bars represent the standard error of the mean. ***p < 0.001, ** p < 0.01, * p < 0.05.*

3.2.5 Data Analysis

The RT refers to the time between the onset of the target and the motor response. Catch trials were eliminated from the analyses. Anticipated responses (participants responding before the target appeared), omission errors (participants did not respond after the target appeared), RT below 50 ms or above 1000 ms and RT out of two standard deviations from the mean RT range were also excluded from the analysis. were also discarded. The remaining correct mean RT for all participants were submitted to a 3 ISI (500, 1500, 2500) × 5 foreperiod (very early, early, expected, late, and very late) mixed analysis of variance (ANOVA).

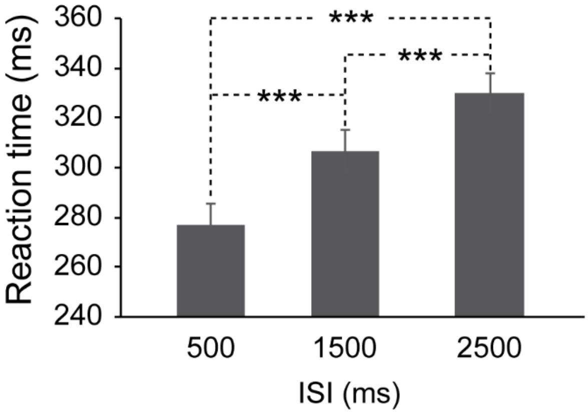


*Figure 3.3. Mean RT for each ISI conditions (500 ms, 1500 ms, 2500ms) collapsed across foreperiods. Error bars represent the standard error of the mean. ***p < 0.001.*

3.3 Results

Detailed RT scores are reported in Table 2.1. We observed were U-shaped expectancy profile in all ISI conditions, with the RT decreasing to a minimum value at the expected moment before subsequently increasing again (see Figure 3.2). 3 ISI (500, 1500, 2500) × 5 Foreperiod (very early, early, expected, late, and very late) ANOVA revealed a main effect of the ISI ($F(2, 28) = 46.042$; $p < 0.001$; $\eta 2 = 0.767$), with the RT were progressively slower with an increase in the ISI (500 < 1500 <2500, all p < 0.001) (Figure 3.3). The ANOVA also revealed the main effect of foreperiod [F (4, 56) = 42.431, p < 0.001, η2 = 0.752], with a significant quadratic effect [F (1, 14) = 133.306, p < 0.001, η2 = 0.905], well captured the effect of temporal expectation.

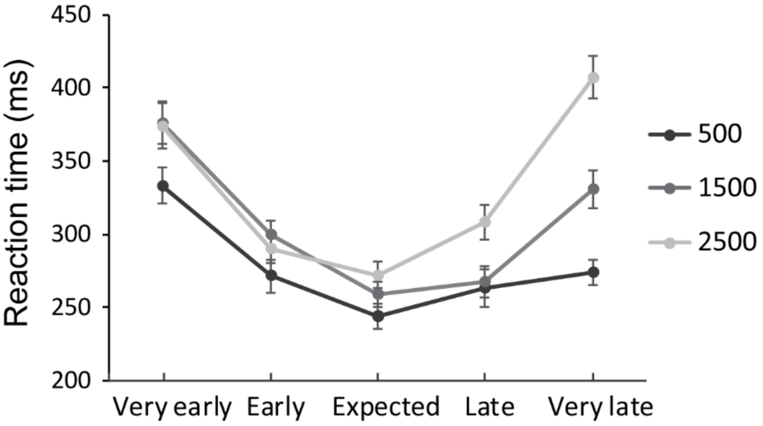


Figure 3.4. Mean RT plotted against each foreperiods during the 500 ms, 1500 ms and 2500 ms ISI conditions.

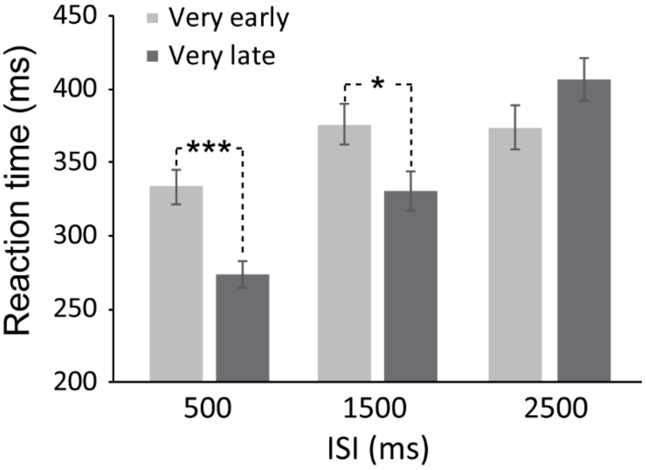


*Figure 3.5. Mean RT for the very early and very late foreperiod during each ISI conditions (500 ms, 1500 ms, and 2500 ms). Error bars represent the standard error of the mean. ***p < 0.001, * p < 0.05.*

The interaction between the ISI and the foreperiod was also significant (F (8, 122) = 10.602; p < 0.001; η2 = 0.431) (Figure 3.4). Pairwise comparisons for expected foreperiod to unexpected foreperiod was showed in Figure 3.2. Pairwise comparisons also revealed that the difference between very early and very late was significant only during 500 ms and 1500 ms ISI, but no difference during 2500 ms ISI condition (Figure 3.5).

3.4 Discussion

U-shaped TEPs was verified in the implicit rhythmic temporal expectation tasks, with faster RT for the expected foreperiods, and progressively slower with the earlier and later unexpected foreperiods (Figure 3.2). However, unlike the symmetric TEPs observed in explicit duration estimation task, the TEPs for rhythmic temporal expectation task were asymmetry during 500 ms and 1500 ms ISI conditions, and the asymmetry gradually diminished during the long ISI condition (Figure 3.4 and Figure 3.5). A possible explanation maybe that, although the temporal expectation generated by the regular rhythms, as the time goes by, the temporal expectations can be further updated by the elapsing time itself. This phenomenon underlying the posterior updating temporal expectation is known as the hazard function, which is explained by increasing conditional probability over time that a target is going to appear given, if it has not already appeared [32, 33, 77]. The hazard function makes use of the flow of time itself to update the expectations on-line, resulted a faster response at later conditions compared with the earlier conditions, leading to an asymmetric TEPs. Interestingly, although we have included 20% catch trials to prevent the conditional probability being used to generate expectation at the later interval [21, 22], our results proposed that the catch trials could have a modulation on the conditional probabilities, but could not completely inhibit the hazard function. Moreover, we observed TEPs for rhythmic temporal expectation task were asymmetry just during 500 ms and 1500 ms ISI conditions, that the difference between very early and very late foreperiod decreasing as the ISI increased (no difference during the long condition). Accordingly proposed that, the duration of the interval between expected and unexpected interval will influence the effect of catch trials. When the participants perceive the target appear as unlikely as time passed, they disengaged their attention and tend to relax their preparation during the later foreperiod. Thus, the longer the interval between expected and later foreperiod, the more likely they expected the trial to be a catch trial.

Gradually slowing down of the RT was related to the ISI timescale increments (Figure 3.3). This finding can be explained according to the scalar timing, that the shorter fixed foreperiod allowed accurate and confident prediction on the upcoming event onset, while for the longer fixed foreperiod, the prediction was more variable and less accurate, with higher time uncertainty, resulting in slower responses [18]. Similar to our finding, previous study using a symbolic cued temporal expectation tasks, with four fixed foreperiods (500 ms, 1000 ms, 1500 ms, 2000 ms), found RT were progressively slower with foreperiod increased [78], However, previous studies about rhythmic temporal expectation task used only two kinds of rhythmic pace [11, 79], we used three different ISI tracked the way in which rhythm-based temporal expectation processing evolved over time more dynamically. Accordingly, we proposed that the range of ISI over which rhythm are perceived is limited, when ISI between the rhythmic stimulus is too shorter, make the rate of the rhythm too slowly, then, the rhythmic structure tends to fall apart, leaving just a series of isolated stimuli. Thus, as the ISI increasing from 500ms to 2500ms, participants tend to have difficult predicting when the target will occur, result in a lengthening of the RT with the increment of ISI timescale.

3.5 Conclusion

We verified U-shaped TEPs for implicit rhythmic temporal expectation task during all the ISI conditions. Moreover, these TEPs was asymmetry during 500 ms and 1500 ms ISI conditions, and gradually become symmetry as ISI grows longer. This founding indicated that although regular rhythms generated temporal expectation effect creating a U-shaped TEPs, as the time goes by, the temporal expectations can be further updated by the elapsing time itself, known as the hazard function, leading to an asymmetry. Further, the effect of hazard function seemed to be attenuated as ISI increasing. In addition, RT was also progressively slower with ISI increased, which suggest that, rhythm perceived is limited, as ISI increasing, rhythmic organization tends to fall apart, difficult to be used to predict upcoming event onset time, result in less stable synchronization performance.

Chapter 4 Does temporal expectation driven by rhythmic cues differ from that driven by symbolic cues?

Summary

Temporal expectation are well known to rely on different sources of predictive information, such as rhythmic and symbolic cues, to direct attention to a future moment in time to optimize behaviour. However, whether temporal expectations driven by rhythmic cues differ from that driven by symbolic cues has not been clearly established. In the current study, 20 participants performed two temporal expectation tasks in which a rhythmic cue or a symbolic cue indicated (70% expected) that the target would appear after an interval of 500 ms (short), 1500 ms (medium) or 2500 ms (long). We observed much sharper expectancy curves and larger cueing effects for the rhythmic cued task than for the symbolic cued task, indicating that rhythmic cues were more effective in improving performance. Furthermore, such differences were only found for the short- but not long-interval condition, revealing that the behavioural differences between the two forms of temporal expectations likely diminished as the time interval increased. Therefore, we propose that the temporal expectation driven by rhythm cues differs from that driven by symbolic cues only in the limited time range; The mechanisms underlying the two forms of temporal expectations become more and more similar over increasing temporal scales.

4.1 Background

Temporal expectation is the ability to focus attention to a future moment in time in order to reduce uncertainty about future events and optimize performance, which is fundamental survival skill to our daily life. For example, crossing a busy street or hitting a tennis ball, accurate prediction of the correct moment to act is crucial; otherwise, an incorrect action will result in a miss or even threaten our survival. Moreover, it has been suggested that temporal expectation can rely on different types of predictive information, such as rhythmic and symbolic cues, to prepare an optimized response at the appropriate point in time [40].

Temporal expectation driven by rhythmic cues, that is, the isochronous presentation of a stimulus sequence, has been related to the dynamic attention model [1, 41]. When participants experience a nonrandom temporal structure, they can spontaneously adapt the temporal regularity to build a temporal pattern of the fixed interval, which can be used to predict the next likely moment of when the next event will occur, so as to optimize perceptual or motor performance. Similarly, the isochronous presentation of a stimulus sequence has been suggested that could entrain (synchronize) attentional processes, the participants give peak performance when the foreperiod (i.e. the interval between the cue and the target) matched the preceding rhythmic interval. The result of this entrainment processing is stimulus-driven attending. Furthermore, several lines of research about rhythm-based temporal attention, have found an inverted U-shaped expectancy profile for perceptual discrimination task, that the performance were improved when the targets occurred at the expected moment compared with the target appeared early or late [5, 41, 65]. In addition, a U-shaped expectancy profile was found for RT speed task, with faster RT for expected foreperiod and slower RT for short or long unexpected foreperiods [80, 81]. The rhythmic cues have been proved to be effective to create temporal expectancies that improve participants' RT performance [11].

In contrast to temporal expectation driven by the rhythmic cues, the temporal expectation driven by the symbolic cues has been interpreted according to the interval models [17, 18]. In which, a clock stage involves a pacemaker emits a continuous stream of pulses between the cue-target interval, then the number of pulse switch serves as a duration code maintained in working memory. Then, at a memory stage, the working memory transferred to a long-term reference memory. At last, at a decision stage, an updated comparison code is generated relative to a remembered standard code, when the current duration code reaches the temporal criterion, “time is up” and the currently timed interval is expected to end. Depending upon the mnemonic representations of the learned cue-target interval, the symbolic cues informs participants whether an upcoming target would likely to appear after a short or long delay [82, 83]. Researches on the temporal expectation driven by symbolic cues have revealed that, comparing to misleading (invalid) and non-informative (neutral) cues, the symbolic cues are proved correctly inform the target onset moment (valid) result in faster and more accurate performance [23, 56, 78, 84-86].

According to the above studies, temporal expectation driven by both rhythmic and symbolic cues have been proved to be effective in optimizing performance. Moreover, these two forms of temporal expectations have been suggested to be distinct by several previous studies [40, 87, 88]. Temporal expectation triggered by rhythmic cue is proposed to be created automatically, exogenously, implying a bottom-up processing [89]. On the other hand, temporal expectation triggered by symbolic cue is proposed to be generated consciously, endogenously, implying a top-down processing [90, 91]. In contrast, Schwartze et al. (2011) applied event-related brain potentials (ERPs) queried the bottom-up process in rhythm-based temporal expectation. Their results showed that rhythmic cue modulated the attention-dependent potential (P3b) when the participants concentrated on the rhythm. While in the session which participants ignored the rhythm, the automatic processing potential (MMN) was not influenced. Thus, they concluded that the influence of regular rhythm was dependent on top-down cognitive processing rather than bottom-up automatic processing [92]. Thus, whether different mechanisms exist between temporal expectations driven by rhythmic and symbolic cues, remains unknown. Moreover, previous studies researched the relationship between the two forms of temporal expectations has just focused on the millisecond range timing. Whether the difference between the two forms of temporal expectations will change as increasing time intervals, has not been clearly established.

The present study aimed to examine, do temporal expectation driven by rhythmic cues differ from that driven by symbolic cues across millisecond and second time range. In the current study, an adaptation of the classical temporal expectation tasks in Trivino et al. (2011) was used, compared the two processes directly. In addition, instead of only one or two interval conditions in the previous studies [11, 56, 79, 87, 88, 93], we used three standard intervals (500ms, 1500ms, 2500ms), so as to investigate both temporal expectations more flexibly and dynamically across millisecond and second range timing. In our tasks, rhythmic cues are manipulated according to the duration of the inter-stimulus interval (ISI) between isochronous successive stimuli, symbolic cues are manipulated according to the association of the digital to one of the three possible standard intervals.

4.2 Methods

4.2.1 Participants

Twenty healthy right-handed students (14 men, 6 women, mean age = 25.7 years, SD = 3.5 years) from the Okayama University participated in the experiment. All participants with normal or corrected-to-normal vision and had no record of neurological or psychiatric disorders. The study was approved by the institutional ethics committee, and all participants provided written informed consent.

4.2.2 Stimuli

E-prime software (Schneider et al., 2002) was used to present stimulus and record behavioural data. Two temporal expectation tasks ware performed by the participants: Rhythmic cued task and Symbolic Cued task. Each trial for both tasks included a fixation point, a temporal cue and a target, all the stimulus were presented at the centre of a 27-in monitor with a grey background (RGB=180,180,180), and a resolution of 1280*720 pixel. The fixation point was a black "+" symbol (0.6°× 0.6° of visual angle with a viewing distance of 60cm). The temporal cue in the rhythmic cued task, was an isochronous sequence contains of circle stimulus appeared and disappeared five, six, or seven times at either a short (i.e. every 500 ms), medium (i.e. every 1500 ms) or long (i.e. every 2500 ms) pace (see Figure 4.1). All the circle stimulus was gray circle (diameter = 1.2°; RGB = 100,100,100), expect for the final stimulus turned white (diameter = 1.2°) to warn about the upcoming target. The temporal cue in the symbolic cued task, was either a digital 500, 1500 or 2500 (Courier New at 18-point size). The digital 500 indicated the target would appear after 500ms, the digital 1500 indicated the target would appear after 1500ms, whereas the digital 2500 indicated the target would appear after 2500ms. In both tasks, the target was a black circle (diameter=1.2°).

4.2.3 Procedure

Participants sat on a comfortable chair in a silent and dimly illuminated room, and their head were fixed with a chin rest. Each participant performed two experimental tasks: rhythmic cued task and symbolic cued task.

Task 1. Rhythmic cued task

A schematic of the rhythmic cued task is provided in Figure 4.1a. Each trial began with the presentation of a fixation point for 500ms. 300ms after the offset of the fixation point, followed by a rhythmic cue which consisted of an isochronous sequence of five, six, or seven stimuli (uniform probability) with a within-block ISI of 500 (short), 1500 (medium), or 2500 (long) ms. Within a trial, the stimuli in the isochronous sequence were all filled gray circles, with a duration of 100ms except for the final stimulus, which was white and served as a warning signal, and the participants were told that the last white circle in the regular sequence marked the beginning of the preparatory interval. The different number of rhythmic stimuli was to prevent the warning signal being fully predictable. In most trials, the white circle followed by a target, a black circle. The target appeared for 100ms after a variable foreperiod (described in the design section). Participants were informed that they could use the rhythmic cue to predict the time of target onset, so as to respond to its appearance as quickly as possible, while avoiding anticipations, by pressing the left button with their index finger. A maximum of 1500ms was allowed to respond. There was a random inter-trial interval of 1500-3500ms.

Task 2. Symbolic cued task

A schematic of the symbolic cued task is provided in Figure 4.1b. The procedure was exactly the same as the rhythmic cued task. Expect that the cue was not an isochronous sequence, but a symbolic cue, which contained of one of the three digitals: 500(short), 1500(medium), or 2500(long). The digital indicated the duration of the foreperiod, cued the participants to expect the target after a short, medium, or long foreperiod. Participants were informed to use of the temporal information carried by the digital cue to predict when the target would appear, so as to respond to its appearance as quickly as possible, while avoiding anticipations, by pressing the left button with their index finger. A maximum of 1500ms was allowed to respond. There was a random inter-trial interval of 1500-3500ms.

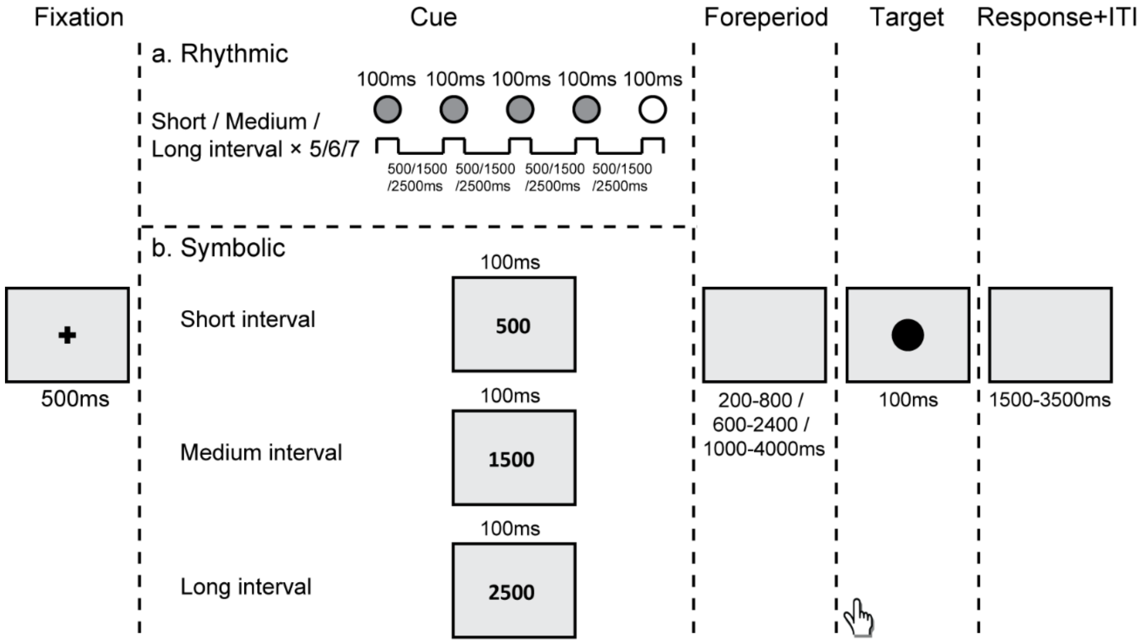


Figure 4.1. Experimental task. a. Rhythmic task. Each trail started with a fixation point, followed by a rhythmic cue which consisted of five, six, or seven stimuli, each 100ms in duration, and presented with 500ms, 1500ms, or 2500ms inter-stimulus interval (ISI). the last white circle cue stimulus served as a warning signal, marked the beginning of the preparatory interval (foreperiod). b. Symbolic cued task. The procedure was almost the same as the rhythmic cued task. Expect that the cue was a symbolic cue, which contained of one of the three digitals: 500(short), 1500(medium), or 2500(long). The digital indicated the duration of the foreperiod. For example, the digital 500 indicated that the target would appeared after a 500ms foreperiod. In both tasks, participant's task was to response to the appearance of the target as quickly as possible. They were encouraged to use the temporal information conveyed by the cue to improve RT.

4.2.4 Design

In both tasks, the target was appeared after an expected foreperiod (500ms / 1500ms

/ 2500ms) in 70% of the trials (expected expectancy level), and the probability for the unexpected foreperiod was set to 20% of the trials, in which two foreperiod (0.4, 0.7 proportion of expected foreperiod) were shorter than the expected foreperiod (very early and early expectancy level), two foreperiod (1.3, 1.6 proportion of the standard interval) were longer than the expected foreperiod (late and very late expectancy level). For example, for the short interval condition, the standard interval was 500ms and the foreperiod were 200, 350, 500, 650, and 800ms. For medium interval condition, the standard interval was 1500ms and the foreperiod were 600, 1050, 1500, 1950, and 2400ms. For long interval condition, the standard interval was 2500ms, and the foreperiod were 1000, 1750, 2500, 3250, and 4000ms (Table 2.1). In 10% of total the trials the target was not presented (catch trials). In “catch” trials, there was no black circle target, but a gray background was displayed after the warning signal.

Table 4.1. Summary of all expected and unexpected foreperiods (ms) for each standard interval (short, medium, and long).

Standard interval	Expected foreperiod (ms)	Unexpected foreperiod (ms)			
		Very early	Early	Late	Very late
Short	500	200	350	650	800
Medium	1500	600	1050	1950	2400
Long	2500	1000	1750	3250	4000

The factorial design had three relevant factors: task (rhythmic or symbolic), standard interval (short, medium, or long) and expectancy level (very early, early, expected, late, or very late). Prior to symbolic cued task, all participants performed a training session with 54 trials to learn the association between the digital cues and the foreperiod. In the training phase, the foreperiod was always expected, for ensuring a stable reference memory. The training session began with blocked presentation (6 trials) of each of the 3 standard intervals condition (500ms, 1500ms, 2500ms). Then followed by a block of 24 trials in which the 3 standard intervals were cyclically presented in an order from 500ms to 2500ms. Finally, a block of 24 trials with random presentation of the 3 standard intervals.

Table 4.2. Mean RT for each task condition (rhythmic cue, symbolic cue), standard interval (500, 1500, and 2500 ms) and foreperiod (very early, early, expected, late, and very late).

	Rhythmic cue (ms)			Symbolic cue (ms)		
	Short	Medium	Long	Short	Medium	Long
Very early	401 (18)	456 (16)	479 (20)	385 (12)	457 (17)	479 (21)
Early	295 (14)	352 (18)	381 (16)	327 (20)	382 (14)	390 (12)
Expected	253 (15)	282 (13)	295 (11)	294 (15)	323 (13)	330 (14)
Late	288 (13)	305 (10)	360 (18)	306 (17)	326 (13)	355(14)
Very late	320 (10)	389 (15)	445 (20)	322 (17)	404 (22)	463 (21)

Values in parentheses are standard errors of the mean.

4.2.5 Data analysis

The RT in both tasks refers to the time between the onset of the target and the motor response. Practice trials and catch trials were eliminated from the analyses. Anticipated responses (participants responding before the target appeared), omission errors (participants did not respond after the target appeared), RTs larger than two standard deviations from the mean RT for each dependent variable and for each participant were also excluded from the analysis.

The remaining correct mean RT were analyzed using a repeated measures ANOVA with a 2 Task (rhythmic cue, symbolic cue) x 3 Standard interval (short, medium, long) x 5 Expectancy level (very early, early, expected, late, and very late) factorial design. The cueing effect, which is an index of attentional benefit, was calculated by subtracting the mean expected RT from each mean unexpected RT (very early, early, late, or very late), and analyzed using repeated measures ANOVA with a 2 Task (rhythmic cue, symbolic cue) × 3 Standard interval (short, medium, long) × 4 Unexpected level (very early, early, late, and very late) factorial design.

4.3 Results

Figure 4.2 shows the RT plotted against the expectancy levels at the short, medium and long standard intervals for the rhythmic, symbolic cued tasks. We observed the RT curves were U-shaped in all conditions, with faster RT for the foreperiods approaching the expected one, increasing with the shorter and longer unexpected foreperiods. Detailed data are presented in Table 2.2. The 2 Task (Rhythmic cue, symbolic cue) × 3 Standard interval (short, medium, long) × 5 Expectancy level (very early, early, expected, late, and very late) repeated-measures ANOVA revealed a main effect of the expectancy level ($F (4, 76) = 115.05$; $p < 0.001$; $\eta2 =0.858$). Further pairwise comparisons confirmed that the RT was fastest at the expected moment compared to the earlier and later unexpected moments (expected < late < early < very late < very early, all $p \leqslant 0.002$), which captured the effect of temporal expectation. There was also a significant main effect of standard interval ($F (2, 38) = 105.16$; $p < 0.001$; $\eta2 =0.825$), RT were progressively slower with the increase of standard interval (short < medium <long, all $p < 0.001$). (Figure 4.3). Moreover, the interaction between the expectancy level and the standard interval was significant (F (8, 152) = 7; $p < 0.001$; η2 =0.239). Separate ANOVAs for each standard interval are presented below. The post hoc analyses revealed a significant difference between the very early and very late expectancy levels at the short and medium standard intervals (short: $p < 0.001$; medium: $p = 0.005$), but no difference was observed for the long standard interval condition (long: $p = 1$) (Figure 4.4).

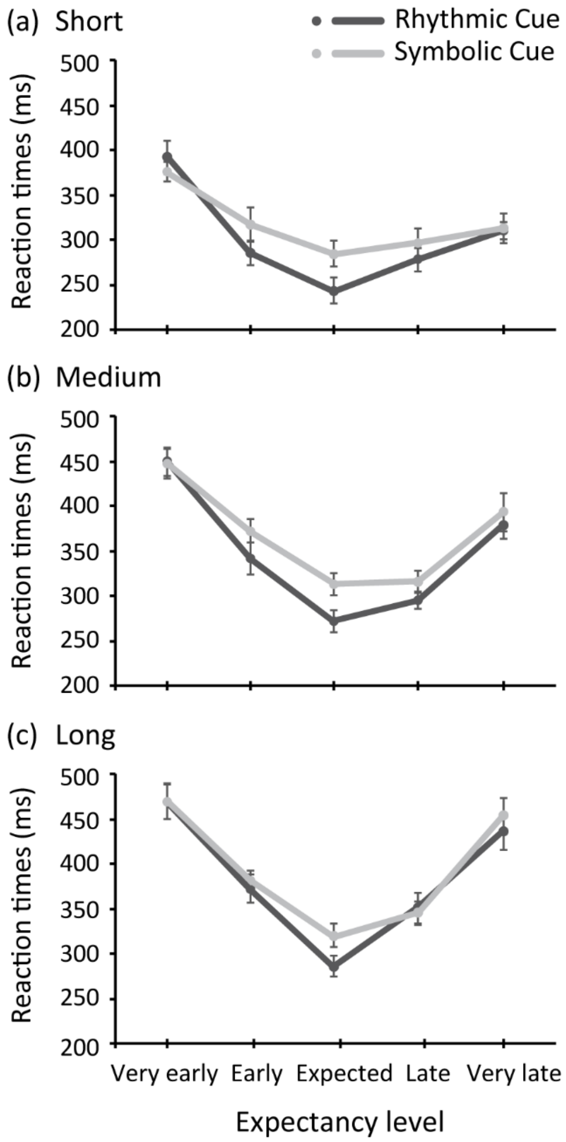


Figure 4.2. Mean RT plotted against the expectancy level for the rhythmic and symbolic cued tasks in the short, medium and long standard interval conditions.

For the short standard interval, a significant main effect was found for the expectancy level (F (4, 76) = 50.828; $p < 0.001$; η2 =0.728). The expectancy level × task interaction was also significant (F (4, 76) = 0.29; p = 0.029; η2 =0.146), such that the U-shaped curves for the rhythmic cued task were sharper than those for the symbolic cued task. For the medium standard interval, a significant main effect was found for the task (F (1, 19) = 6.004; p = 0.024; η2 =0.24) and the expectancy level (F (4, 76) = 54.079; $p < 0.001$; η2 =0.74). The expectancy level × task interaction did not reach significance. For the long standard interval, the only significant main effect was found for the expectancy level (F (4, 76) = 60.440; $p < 0.001$; η2 =0.761); no other main effects or interactions were significant. To summarize, the expectancy level × task interaction was significant at the short interval but not at the medium and long intervals (Figure 4.2).

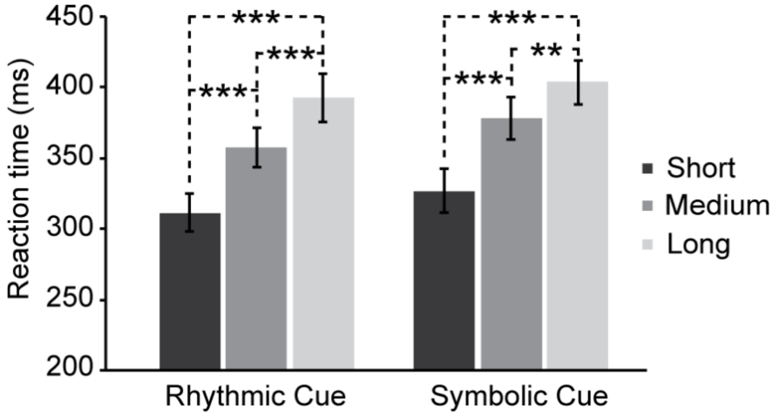


*Figure 4.3. Mean RT for rhythmic and symbolic cued tasks in each standard interval condition (short, medium, and long) collapsed across expectancy levels. Error bars represent the standard error of the mean. ***$p < 0.001$, ** $p < 0.01$.*

Regarding the attention benefit for each task, the data were reexamined in terms of the cueing effect (i.e., the difference between the expected trial and each type of unexpected trial) instead of the mean RT (see Figure 4.5). The 2 $_{\text{Task}}$ (rhythmic cue, symbolic cue) × 3 $_{\text{Standard interval}}$ (short, medium, long) × 4 $_{\text{Unexpected level}}$ (very early, early, late, and very late) ANOVAs showed a main effect of the task (F (1, 19) = 14.2; p = 0.001; η2 =0.428), with a larger cueing effect for the rhythmic cued task than for the symbolic cued task. The main effects of the unexpected level (F (3, 57) = 85.8; p < 0.001; η2 =0.819) and standard interval (F (2, 38) = 15.7, p < 0.001; η2 =0.453) were also significant. Moreover, the interaction between the unexpected level and the standard interval was significant (F (6, 114) = 5.5, p < 0.001; η2 =0.224). Separate ANOVAs for each standard interval are presented below.

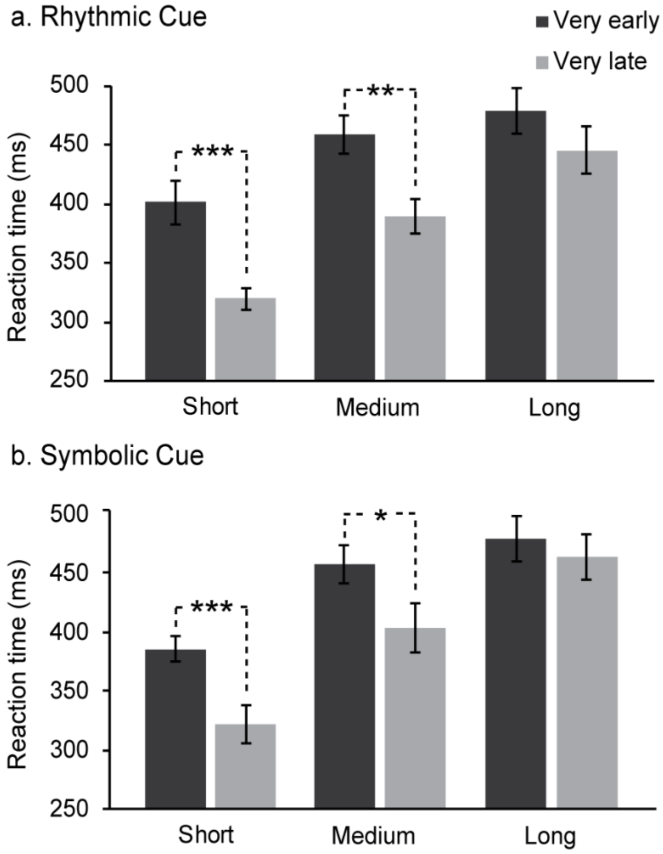


*Figure 4.4. Mean RT for the very early and very late expectancy levels for both the rhythmic and symbolic cued tasks in each standard interval condition (short, medium, and long). Error bars represent the standard error of the mean. ***p < 0.001, ** p < 0.01, * p < 0.05.*

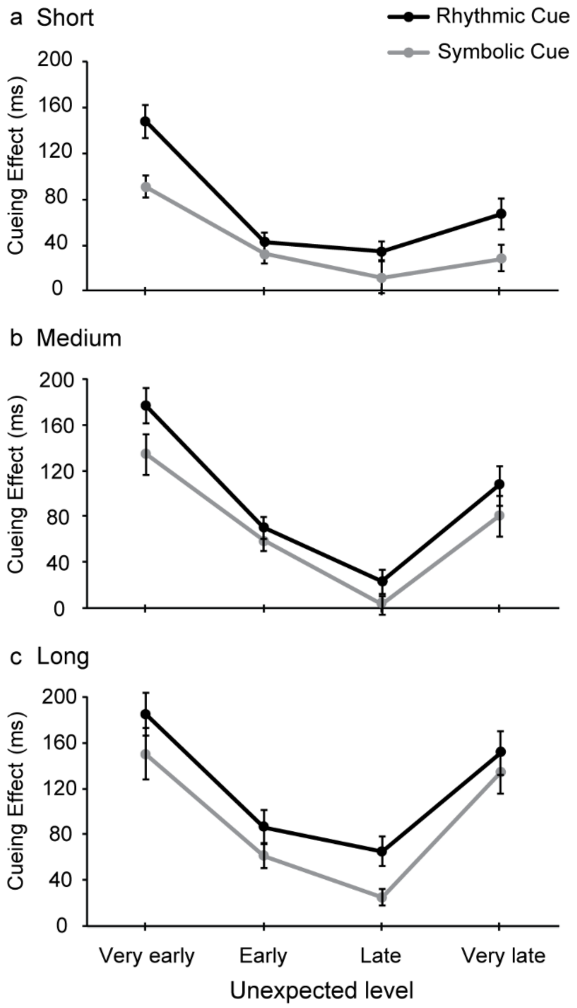


Figure 4.5. Cueing effects (each unexpected RT minus the expected RT) as a function of the unexpected level and task (rhythmic cue and symbolic cue) for the short, medium and long standard intervals.

For the short standard interval, a significant main effect was observed for the task (F (1, 19) = 13.05; p = 0.002; η2 =0.407) and the unexpected level (F (3, 57) = 43.4; p < 0.001; η2 =0.696). For the medium standard intervals, a significant main effect was also observed for the task (F (1, 19) = 7.93; p = 0.011; η2 =0.295) and the unexpected level (F (3, 57) = 41.07; p < 0.001; η2 =0.684). For the long standard interval, the only significant main effect was found for the unexpected level (F (3, 57) = 39.11; p < 0.001; η2 =0.673); no other main effects or interactions were significant. To summarize, the main effect of the task (i.e., a larger cueing effect for the rhythmic cued task) was only observed at the short and medium standard intervals and not at the long interval (Figure 4.6).

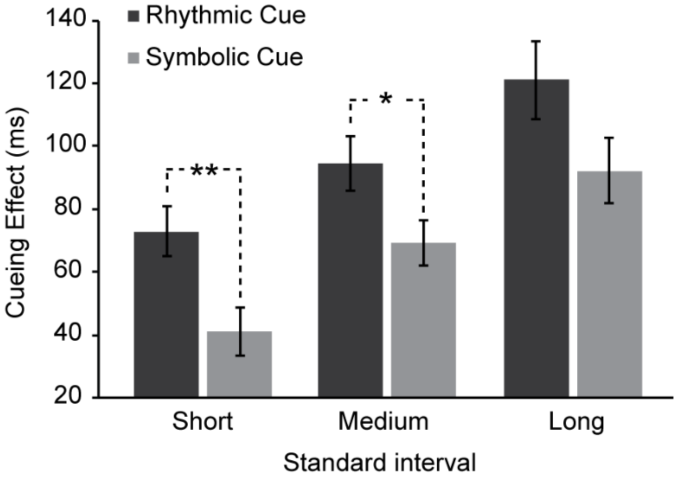


*Figure 4.6. Cueing effects (RT unexpected -RT expected) for the rhythmic and symbolic cued tasks in the short, medium and long standard interval conditions collapsed across the unexpected level. Error bars represent the standard error of the mean. **p < 0.01, * p < 0.05.*

4.4. Discussion

The current study used a single experimental design, directly compared the rhythmic and symbolic cued temporal expectation tasks. The results showed that temporal expectation triggered by the rhythmic cues can focus more concentrated resources on the short-expected interval, moreover rhythm-based temporal expectation is likely to be more effective in optimizing behavior performance, such that the U-shaped curves for rhythmic cued task was sharper and the cueing effect for the rhythmic cue was larger than the symbolic cue. Furthermore, the behavioral differences between the two forms of temporal expectations were diminished with increasing time interval.

U-shaped RT curves was verified in both rhythmic and symbolic cued temporal expectation tasks, with faster RT for the expected foreperiods, and progressively slower with the shorter and longer unexpected foreperiods (Figure 4.2). This pattern is consistent with previous studies, by used the task in which a symbolic cue or regular context provided information about when a target would occur, observed the reaction time was faster during a temporal window close to the expected foreperiod, and increased outside this temporal window for earlier and later unexpected interval, resulting in a U-shaped RT curve [11, 86]. This window also been assumed as the "temporal window of expectancy", means the events falling within this temporal window are highly subjected to the same attentional benefits as the events occurring exactly at the expected time point [88]. Additionally, by directly compared two tasks, our results showed the curves for rhythmic cued task are sharper than symbolic cued task in the short and medium conditions, which indicating that the rhythmic cues direct attention to a narrow time window in which the target is expected to occur, leading to a more precise attentional targeting in time for rhythmic cued temporal expectation processing. Further experiments could try to employ more types of expectancy level to quantify the size of this window relative to rhythmic and symbolic cued temporal expectation task.

Notably, further comparisons revealed asymmetric curves for both tasks had longer RT for the earlier foreperiod than for the later foreperiod, and the asymmetry gradually diminished with the standard interval increased (Figure 4.4). As we proposed in the chapter 3, the possible explanation maybe the reliance on the "hazard function", which is defined as increasing conditional probability over time that a target is going to appear if it has not already appeared [32, 33, 77]. Consistent with the previous study found the reaction time faster when the target appeared after the later than the earlier foreperiod [86]. These results showed that the participants had used the temporally probability information inherent in the elapse of time itself, reoriented their attention to the later foreperiod if the target didn't appear at expected interval. Similar to the founding in chapter 3, we observed the difference between very early and very late expectancy level decreasing as the standard interval increased (no difference at the 2500 ms condition). Evidence that in both rhythmic and symbolic cued task, when the participants perceive the target appear as unlikely as time passed, they disengaged their attention and tend to relax their preparation during the later foreperiod. Thus, the longer the interval between expected and later foreperiod, the more likely they expected the trial to be a catch trial. However, further research is needed to verify our supposition.

Lengthening of the RT was related to the timescale increments in both task (Figure 4.3). This finding can be explained as the shorter constant foreperiod allowed accurate and confident prediction on the target onset time, while for the longer constant foreperiod, the prediction was more variable and less accurate, with higher time uncertainty, resulting in slower RT [18]. Similar to our finding, previous study using a cued reaction time task, upon the presentation of a symbolic cue, participants could predict the onset of the target after one of four different foreperiods (500 ms, 1000 ms, 1500 ms, 2000 ms) with 100% certainty, they found that RT were progressively slower with foreperiod increased, and the RT were significantly fastest at the shortest foreperiod[78]. However, previous studies about rhythmic cued task always used only two kinds of rhythmic pace, provided that participants responding faster after the fast rhythmic pace than after the slow rhythmic pace [11, 79]. This time we used three conditions (500 ms, 1500 ms, 2500 ms), proved this pattern for temporal expectation driven by rhythmic cues more generally. In addition, by observed U-shaped curves at all the standard interval conditions (short, medium long) for both rhythmic and symbolic cued task, compared with the previous studies found validity effects at only short interval conditions [87, 94]. we further supported the flexibility and dynamicity of the expectation mechanism involved.

The greater effectiveness of rhythmic than symbolic cues meant that the rhythmic cue was most likely more reliable and predictive than the symbolic cue (Figure 4.5 ad Figure 4.6). The effect of temporal orienting of attention has been investigated separately in studies using rhythmic cues [11, 79, 93, 95, 96] as well as symbolic cues [78, 83, 86, 96]. However, the effectiveness of the two types of temporal expectation has been rarely directly compared. The present study provides the evidence that the magnitude of cueing effect for the rhythmic cued task was greater than the symbolic cued task, reflecting the rhythmic cue was likely to be more reliability and predictive than symbolic cue. Although Trivino (2001) also compared the rhythmic and symbolic cued RT tasks, and showed no differences between tasks [94]. The reason can be due to the small sample of only five participants and the difficulty of the target design in the previous study contained both go and no-go target. Accordingly, the conceivable interpretation for our results maybe that the source of rhythm-based temporal expectation is a self-sustaining entrainable oscillator [1]. However, the source of temporal expectation driven by symbolic cue is relative to a remembered standard code in the long-term reference memory. As the long-term memory storage cannot become self-sustaining immediately. Rather, a period of time is required to become consolidated, and the memory can be strength or weaken by various modulating influences. Thus, the symbolic cued temporal expectation processing with greater variability leads to a weak memory of the interval, in turn poor performance. On the contrary, rhythmic cue can more precisely and stably direct attention to the target onset moment and speed up response time more effectively.

As a final point, we found the significant behavioral difference between rhythmic and symbolic cued temporal expectation task, such that U-shaped RT curves for rhythmic cued task were sharper than symbolic cued task, and the cueing effect for rhythmic cue was larger than the symbolic cue, were just observed at the short and medium standard interval condition, but no difference was found at long interval condition. One conceivable explanation is that the range of tempi over which rhythms are perceived is limited [97]. If the rhythms are too slow, the synchronization performance will become less stable, and the variability will be also increased, rhythmic organization tends to gradually fall apart, leaving only a series of isolated stimulus. The slow rhythms limit has also been linked to the temporal capacity of working memory[98, 99]. Thus, we suppose that, maybe the dissociation between temporal expectation triggered by rhythmic and symbolic cues can be only established at a limited range of time intervals. However, this span of the limit remains to be investigated in the further study.

4.5. Conclusions

By observed U-shaped RT curves for both rhythmic and symbolic cued tasks in all the standard interval conditions, we verified the temporal expectations can be flexibly created by multiple regular rhythms and symbolic cues. Moreover, by directly compared rhythmic and symbolic cued temporal expectation by means of a single experimental design. The results show much sharper U-shaped RT curves and larger cueing effects for rhythmic cued task compared to symbolic cued task at the short standard interval, indicating that rhythmic cues more precisely and stably direct attention to the event onset moment and are more reliable and effective in optimizing behavioral performance, over a limited range of time intervals. Crucially, no difference was found between the two forms of temporal expectation during the long interval, revealing that the behavioral differences between temporal expectations triggered by rhythmic and symbolic cues diminished as the time interval increased. Overall, we propose that it is difficult to affirm whether temporal expectations driven by rhythmic and symbolic cues have the same or different mechanisms, the distinction between the two forms of temporal expectation will change with timescales.

Chapter 5 Neural dissociation between temporal expectation driven by symbolic cues and passage of time by: Evidence from event-related brain potentials.

Summary

Temporal expectation can be externally driven by the symbolic cue (temporal orienting effect), also can be internally driven by the passage of time (foreperiod effect). However, the relationships between the two forms of temporal expectations still unclear, whether they can work in parallel and have distinguishable neural signature remain unanswered. In the current study, behavioural results observed both temporal orienting and foreperiod effect, with faster responses at the expected and late compared to early foreperiod, but no difference between expected and late foreperiod during both short and long interval conditions. Crucially, Electrophysiological results showed evidence of two distinct temporal expectation processes, as the two forms of temporal expectation seem to affect different stages of stimulus processing, a linear foreperiod effect was observed affects processing earlier than the expectation based on symbolic cues with a U-shaped pattern. Furthermore, this study shows that temporal expectation driven by symbolic cues and passage of time can work in parallel with distinguishable neural signatures.

5.1 Background

Making temporal expectation is central to our every life. Introduced in the introduction chapter, symbolic cues, if available, passage of time itself are two sources of information that humans can use to form temporal expectation.

Temporal expectation can be externally driven by the symbolic cue, refers to the ability to voluntarily pre-directing attention to a particular moment [21, 83]. Thus, when we predict an event to occur at an expected moment, we will get prepare for it, and response faster to the event. This effect relates to the temporal orienting (TO) effect. This effect has been experimentally studied used posner paradigm [100]. In this classical task, a symbolic cue provides temporal information about when the target will appear, after a short or long foreperiod (the interval between cue and target). The cue may be valid (i.e. short cue-short foreperiod) or invalid (i.e. short cue-long foreperiod) indicating the target onset moment. The temporal orienting effect is observed as a faster response when the cue is valid compared to invalid [23, 101, 102].

In contrast, temporal expectation based on the passage of time itself has been suggested internally driven temporal expectation exploits the unidirectional flow of time itself, conditionally and intrinsically biasing event predictability [27, 30, 103]. Imaging waiting a bus at the station, the probability of bus arrive will increase as long as you wait for it. The longer you wait, the more your expectation grow. This ever-heightening temporal expectation illustrates the phenomenon of “hazard function”, which is defined as the increasing conditional probability over time that an event will appear given that it has not already appeared. A classic example of temporal expectation based on passage of time is the variable foreperiod effect (FP), a faster detection and discrimination responses as increasing the foreperiod [25, 29].

The relationships between the two forms of temporal expectation has been considered only recently. Correa et al., 2006 suggested strong interactions rather than dissociations between temporal orienting and foreperiod effects [22]. Trivino et al., 2010 also confirmed the association between temporal orienting and foreperiod effects, supported the voluntary and strategic nature of the two forms of temporal expectation, which depend on the prefrontal cortex, suggested a common mechanism[24]. However, neuroimaging studies using fMRI provided dissociable evidence that temporal expectation driven by the symbolic cues entails a left sensorimotor cortical circuit, including the premotor (PMA), supplementary motor (SMA) and inferior parietal (IPC) areas [104-108], while, with regard to the temporal expectation driven by the passage of time, a pivotal role of right lateral pFCs has been hypothesized[35, 36, 109-112]. Moreover, by manipulated both temporal orienting and foreperiod effect within a factorial design, Coull et al. 2016 proposed that, temporal expectation driven by symbolic cues activated left inferior and superior parietal cortices, while temporal expectation driven by the passage of time activated left intraparietal sulcus and right inferior frontal cortex, differentiate discrete mechanism in distinct brain regions[78]. Therefore, the relationships between the two forms of temporal expectations still unclear, whether they can work in parallel and have distinguishable neural signature remain unanswered.

Aforementioned two forms of temporal expectation have been proved yield dissociable result patterns. U-shaped pattern with faster response at the expected moment than earlier or later foreperiod were observer in symbolic cued temporal expectation task. Linearly increasing pattern with faster response with increasing foreperiod was observed in the foreperiod effect. Thus, the U-shaped and lineally increasing pattern of results are thus indicative of the two forms of temporal expectation, respectively. In the current study, we hypothesize two possible outcomes. Any processing driven by the symbolic cues show an enhanced or attenuated sensory components for expected compared to early and late conditions, corresponding to the U-shaped temporal orienting effect. Any processing driven by the passage of time show an enhanced or attenuated sensory components for late compared to expected and early conditions, corresponding to the linear pattern.

5.2 Methods

5.2.1 Participants

A total of 13 volunteer participants (10 males and 3 females) mean age of 28.3 years (range:23-33) from the Okayama University participated in the study. They had normal hearing and had no record of psychiatric disorders. The study was approved by the institutional ethics committee, and all participants gave written informed consent before being enrolled.

5.2.2 Stimuli

Each trial consisted of an auditory cue and target. The cue was either a high (880Hz) or a low (220Hz) triangle tone (200ms). The target was either a violin tone (440Hz, 200ms) or a piano tone (440Hz, 200ms). All auditory stimulus originated from two loudspeakers that were hidden by a black curtain. They were positioned 50 cm from the left front and right front of the participants, with a sound pressure level (SPL) of 70 dB.

5.2.3 Procedure

Participants were seated comfortably in a quiet, dimly-lit room. They were first familiarized with the stimuli and task. To clarify the association between cue and the foreperiod they predicted, four practice blocks was conducted. The first practice block contained only short cue and expected foreperiod, the second practice block contained only long cue and expected foreperiod. The foreperiod was always expected, for ensuring a stable reference memory. The third practice block contained short cue and all the experimental foreperiod (540 ms, 900 ms, 1260 ms). The fourth practice block contained long cue and all the experimental foreperiod (960 ms, 1600 ms, 2240 ms). Each practice block contained 20 trials.

The main experiment consisted of 20 blocks. Each block consisted of 60 trials. A schematic of the task is provided in Figure 5.1. The cue indicated the duration of the foreperiod, cued the participants to expect the target after a short (900 ms) or long (1600 ms) foreperiod. The assignment of the high or low cue tone to the short or long foreperiod was counterbalanced across participants. Participants' task was to press the button #1 to violin tone (50%), press the button #2 to piano tone (50%) as quickly and as accurately as possible. The assignment of target to response was counterbalanced across participants. On 60% of the trials, the target appeared at the expected foreperiod (900 ms or 1600 ms). On 20% of the trials, the target appeared earlier than expected (0.6 proportion of expected foreperiod). On 20% of the trials, the target appeared later than expected (1.4 proportion of expected foreperiod). The next trial began until a response was made or 1200 ms intertrial interval (ITI).

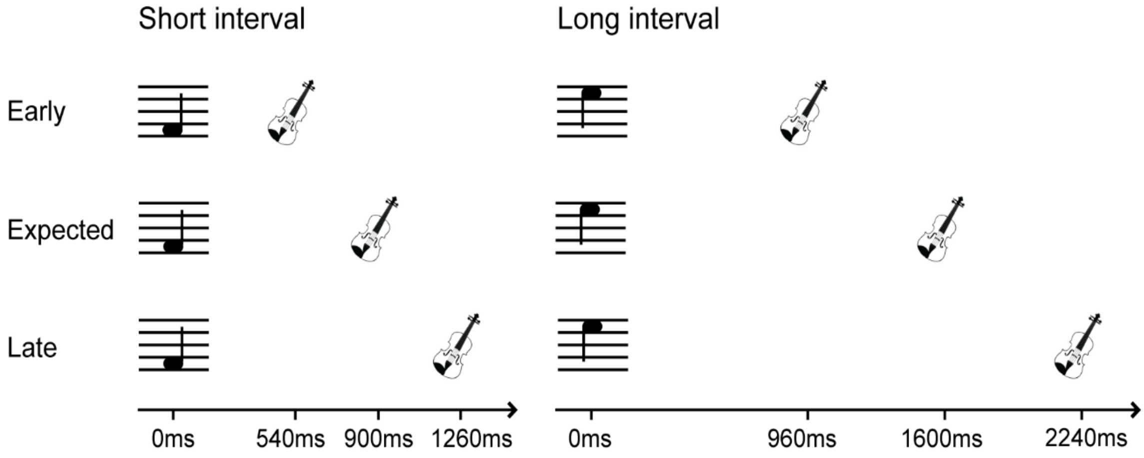


Figure 5.1. schematic outline of task. Each trial started with high or low cue-tone. The cue was followed after a short (left) or long (right) interval by a target (piano or violin tones). Targets appeared either at the expected moment indicated by the cue, or at the unexpected moment (early or late). Participants were instructed to press the button #1 to violin tone, or button #2 to piano tone as quickly and as accurately as possible.

5.2.4 ERP recording

We used E-prime software (Schneider et al., 2002) to present stimulus. An EEG system (BrainAmp MR plus, Gilching, Germany) was used to record EEG signals through 32 electrodes mounted on an electrode cap (Easy Cap, Herrsching-Breitbrunn, Germany). All electrodes were referenced to left and right earlobe. Horizontal eye movements were detected by deriving the electrooculogram (EOG) from one electrode placed approximately 1cm from the outer canthi of the left eye. Vertical eye movements were measured by deriving the EOG from an electrode placed about 1.5 cm below the subject's left eye. The impedances were kept below 5 kΩ. Raw signals were acquired at a sample rate of 500Hz and stored for off-line analysis.

5.2.5 Data analysis

Behavioral data

The RT (reaction time) refers to the time between the onset of the target and the motor response. Practice trials were eliminated from the analyses. The behavioural analysis of RT included correct trials only, RT below 50 ms or above 1000 ms were also excluded from the analysis. RTs out of two standard deviations from the mean RT range were also discarded. The remaining correct mean RT and the percentage of correct responses for all participants were submitted to a 2 Interval (short, long) x 3 foreperiod (early, expected, late) mixed analysis of variance (ANOVA).

ERP data

The ERPs elicited by the task-irrelative stimuli were analyzed by using the Brain Vision Analyzer software (version 1.05, Brain Products GmbH, Munich, Germany). The data were filtered with a butterworth Zero Phase filter (0.1 to 30Hz, 24dB/oct). Data were segmented started 200 ms prior to the target onset and ended 600 ms after target onset. A strict baseline correction from 0 to 50ms was performed to minimize misalignments of the waveforms based on anticipatory neural activity [15, 101, 113].

Trials with artifacts were rejected based on a threshold of ±100 μV in all channels before averaging. Epochs were averaged separately across all participants for each interval and each foreperiod conditions in each electrode.

Electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 were chosen for statistical analyses. Mean amplitudes average for all participants were calculated for the time range 78-118 ms, 158-198ms and 216-256 ms. The first interval was centred on the peak of the N1 (98ms, averaged across all conditions), 40ms interval was selected based on the similar previous studies about temporal expectation on auditory N1 processing [114-116]. The second and third interval followed the N1 or P2 window whilst not overlapping and was centred on the peak of the P2 (178ms, averaged across all conditions) and N2 (236 ms, averaged across all conditions).

Table 5.1. Mean reaction time and proportions of correct responses for each interval (500, 1500, and 2500 ms) and foreperiod (very early, early, expected, late, and very late).

Foreperiod	Reaction time (ms)		Proportion correct	
	Short	Long	Short	Long
Early	463 (18)	477 (19)	0.94 (0.01)	0.94 (0.01)
Expected	432 (20)	457 (19)	0.94 (0.01)	0.94 (0.01)
Late	438 (21)	469 (18)	0.94 (.0.01)	0.94 (0.01)

Values in parentheses are standard errors of the mean.

Separately for each time range, a repeated measures ANOVA was conducted involving the factors 2 Interval (short, long) x 3 Foreperiod (early, expected, late) x 9 Electrode (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). In order to explore whether any temporal expectation effect was driven by the conditional probability (passage of time) or symbolic cues, a linear and quadratic trend analysis was performed using within-subjects contrasts. The Greenhouse-Geisser correction was applied in order to account for the violation of the sphericity assumption.

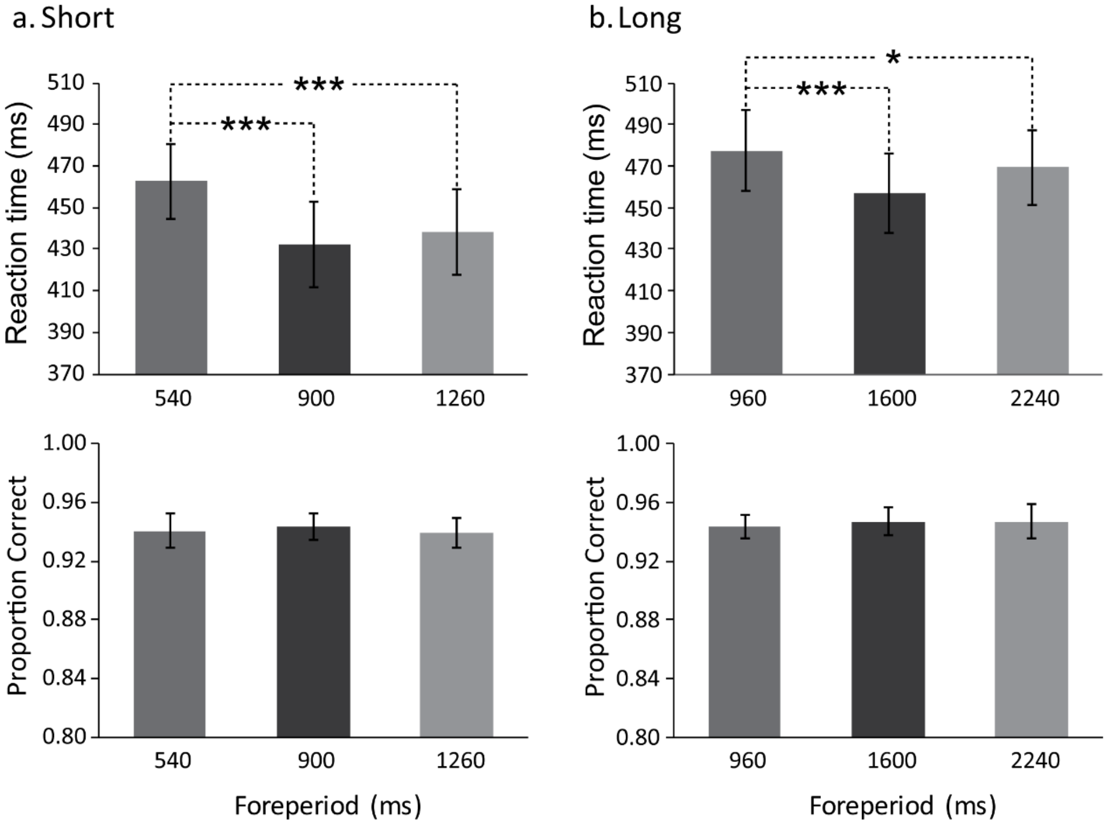


*Figure 5.2. Mean RT for each foreperiod during short and long interval. Error bars represent the standard error of the mean. ***p < 0.001, * p < 0.05.*

5.3 Results

5.3.1 Behavioral Data

Table 4.1 provides an overview of the behavioral data. RT analysis revealed a main effect of the Interval [F (1, 12) = 38.37, p < 0.001, η2 = 0.76], with RT significantly shorter in short (444.5 ms) than long (468 ms) interval trials. The ANOVA also revealed the main effect of Foreperiod [F (2, 24) = 14.18, p = 0.001, η2 = 0.54], well captured the effect of temporal expectation (Figure 5.2). There was no interaction between Interval × Foreperiod. Analysis of the percentage of correct responses revealed no effect of Interval, Foreperiod, or interaction between Interval × Foreperiod.

5.3.2 ERP Data

N1 time range (78-118 ms)

There was a main effect of interval [F (1, 12) = 128.29, p < 0.001, η2 = 0.91], with larger negative amplitude in the short compared to the long interval. The main effect of foreperiod [F (2, 24) = 7.65, p = 0.009, η2 = 0.39], and Electrode [F (8, 96) = 30.63, p < 0.001, η2 = 0.72] was also significant. There was also an interaction between Interval × Electrode [F (8, 96) = 6.37, p = 0.009, η2 = 0.35] and between Foreperiod × Electrode [F (16, 192) = 5.76, p = 0.001, η2 = 0.32] (see Figure 5.6 and Figure 5.7).

The significant interactions between interval and electrode and foreperiod and electrode justified separate analyses for the F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 electrode. The amplitudes of N1 were more negative for short than long interval condition for all the electrodes except P3 and P4 electrode when the target appeared early than expected (see Figure 5.3); the amplitudes of N1 were more negative for short than long interval condition for all the electrode when the target appeared at the expected moment (see Figure 5.4); the amplitudes of N1 were more negative for short than long interval condition for all the electrodes except P3, Pz and P4 electrode when the target appeared late than expected (see Figure 5.5).

Separately analyses for each electrode also showed a main effect of foreperiod [F (2, 24 = 6.55, p = 0.014, η2 = 0.35], with a significant linear trend [F (1, 12 = 7.93, p =

0.016, η2 = 0.4] whilst no quadratic trend [p = 0.88, η2 = 0.002] at the F3, Fz, C3, Cz electrodes during short interval conditions (see Figure 5.8a). There was also a main effect of foreperiod [F (2, 24 = 8.67, p = 0.003, η2 = 0.42], with a significant linear trend [F (1, 12 = 12.14, p = 0.005, η2 = 0.5] whilst no quadratic trend [p = 0.62, η2 = 0.02] at the F3, Fz, C3, Cz electrodes during long interval conditions(see Figure 5.9a).

P2 time range (158-198ms)

There was a main effect of Electrode [F (8, 96) = 9.07, p = 0.001, η2 = 0.43], and an interaction between Foreperiod × Electrode [F (16, 192) = 4.16, p = 0.007, η2 = 0.26].

Separately analyses for each electrode also showed a main effect of foreperiod [F (2, 24 = 4.61, p = 0.037, η2 = 0.28], with a significant quadratic trend [F (1, 12 = 7.68, p = 0.017, η2 = 0.39] whilst no linear trend [p = 0.08, η2 = 0.023] at the Fz, Cz electrodes, and a main effect of foreperiod [F (2, 24 = 10.55, p = 0.001 η2 = 0.47], with a significant linear trend [F (1, 12 = 16.39, p = 0.002, η2 = 0.58] whilst no quadratic trend [p = 0.15, η2 = 0.17] at the P4 electrodes, during short interval conditions (see Figure 5.8b). There was also a main effect of foreperiod [F (2, 24 = 3.967, p = 0.032, η2 = 0.25], with a significant linear trend [F (1, 12 = 4.31, p = 0.036, η2 = 0.26] whilst no quadratic trend [p = 0.5, η2 = 0.04] at the P4 electrodes during long interval conditions (see Figure 5.9b).

N2 time range (216-256 ms)

There was a main effect of interval [F (1, 12) = 32.79, p < 0.001, η2 = 0.73], with larger negative amplitude in the short compared to the long interval. The main effect of foreperiod [F (2, 24) = 7.65, p = 0.025, η2 = 0.31], and Electrode [F (8, 96) = 9.1, p = 0.001, η2 = 0.43] was also significant. There was also an interaction between Interval × Electrode [F (8, 96) = 4.11, p = 0.023, η2 = 0.26] and between Interval × Foreperiod [F (2, 24) = 47.93, p = 0.007, η2 = 0.34].

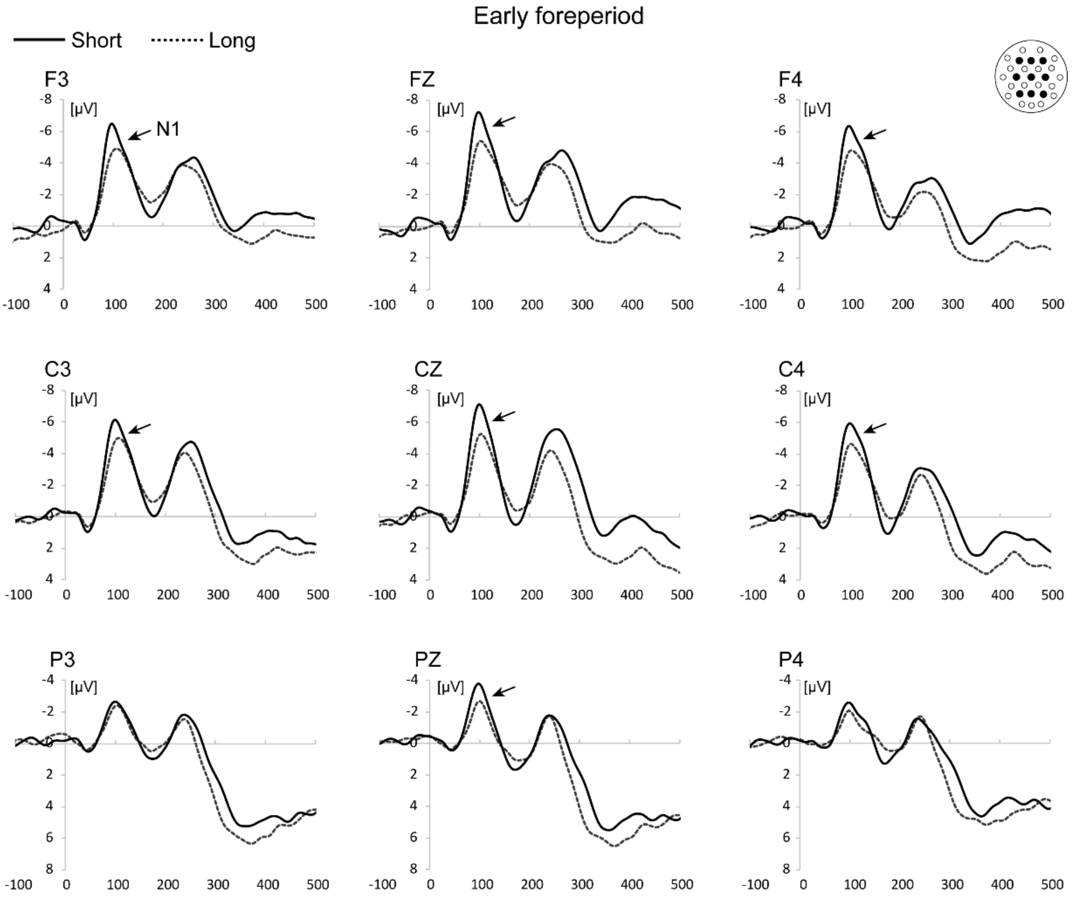


Figure 5.3. Grand average ERPs elicited by target stimuli in the short (solid lines) and the long interval (dotted lines) at the early foreperiod conditions. The electrode configuration is shown on right top, with the presented electrodes marked black. All tracings are aligned with respect to a 0-50 ms baseline. The arrows pointing the N1 potential mark a significant difference between the mean amplitude of the N1 for short and long interval condition. Negativity is up.

The significant interactions between interval and electrode justified separate analyses for the F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 electrode. The amplitudes of N2 were more negative for short than long interval condition for all the electrode when the target appeared at the expected moment (see Figure 4.4); the amplitudes of N1 were more negative for symbolic than long interval condition for all the electrodes except P3 and P4 electrode when the target appeared late than expected (see Figure 5.5).

Separately analyses for each electrode also showed a main effect of foreperiod [F (2, 24 = 6.7, p = 0.007, η2 = 0.36], with a significant quadratic trend [F (1, 12 = 12.27, p = 0.004, η2 = 0.51] whilst no linear trend [p = 0.07, η2 = 0.25] at the C3, Cz electrodes during short interval conditions (see Figure 5.8c).

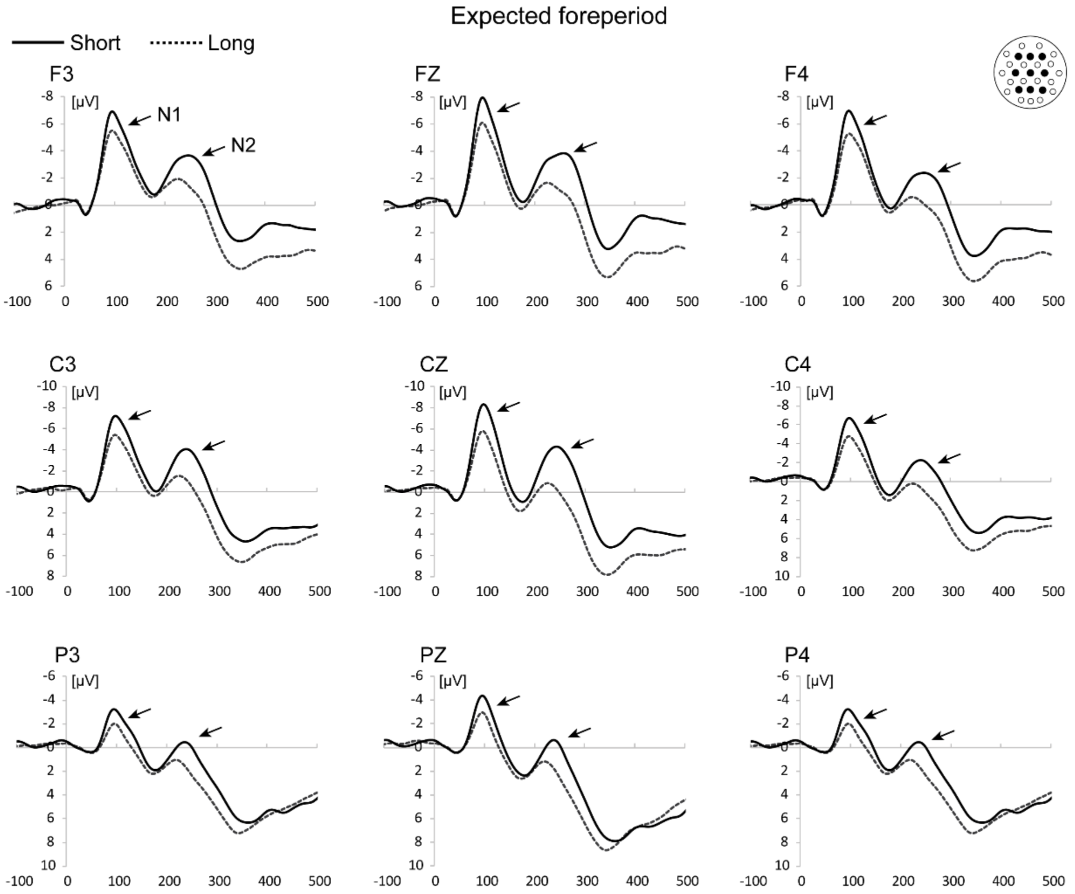


Figure 5.4. Grand average ERPs elicited by target stimuli in the short (solid lines) and the long interval (dotted lines) at the expected foreperiod conditions. The electrode configuration is shown on right top, with the presented electrodes marked black. All tracings are aligned with respect to a 0-50 ms baseline. The arrows pointing the N1 and N2 potential mark a significant difference between the mean amplitude of the N1 and N2 for short and long interval condition. Negativity is up.

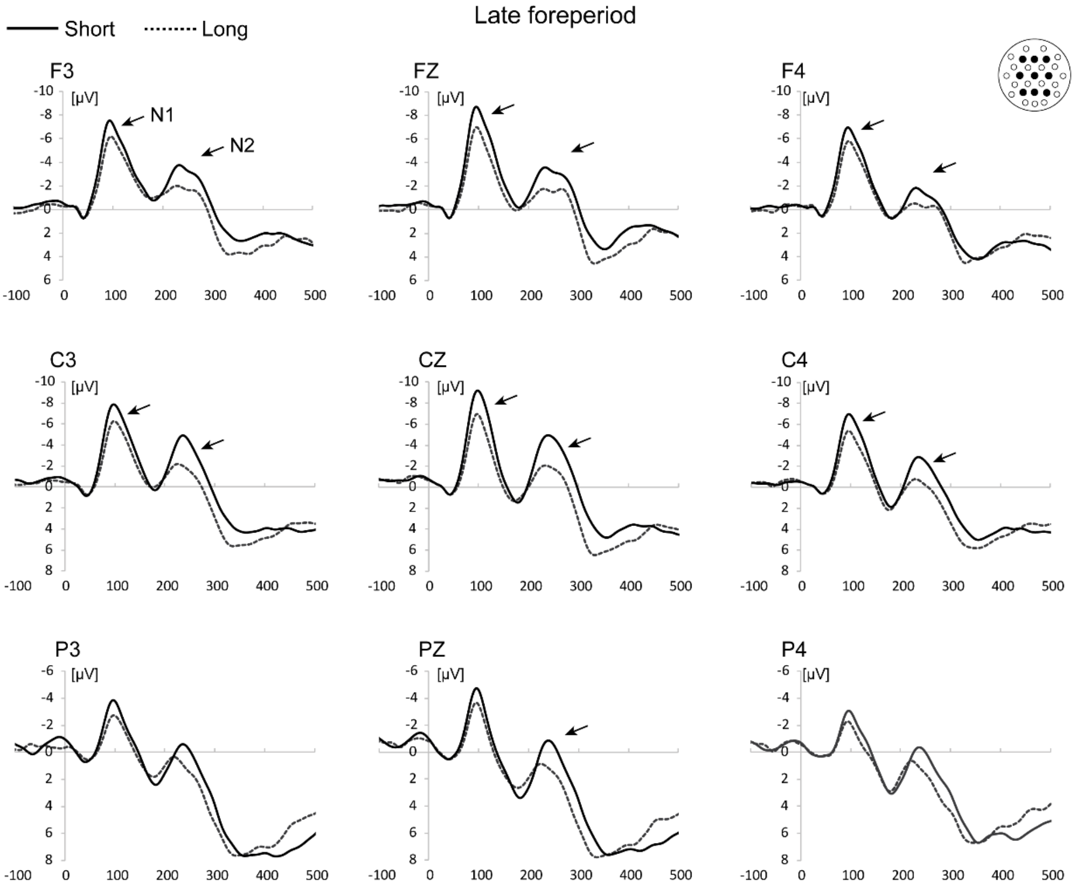


Figure 5.5. Grand average ERPs elicited by target stimuli in the short (solid lines) and the long interval (dotted lines) at the late foreperiod conditions. The electrode configuration is shown on right top, with the presented electrodes marked black. All tracings are aligned with respect to a 0-50 ms baseline. The arrows pointing the N1 and N2 potential mark a significant difference between the mean amplitude of the N1 and N2 for short and long interval condition. Negativity is up.

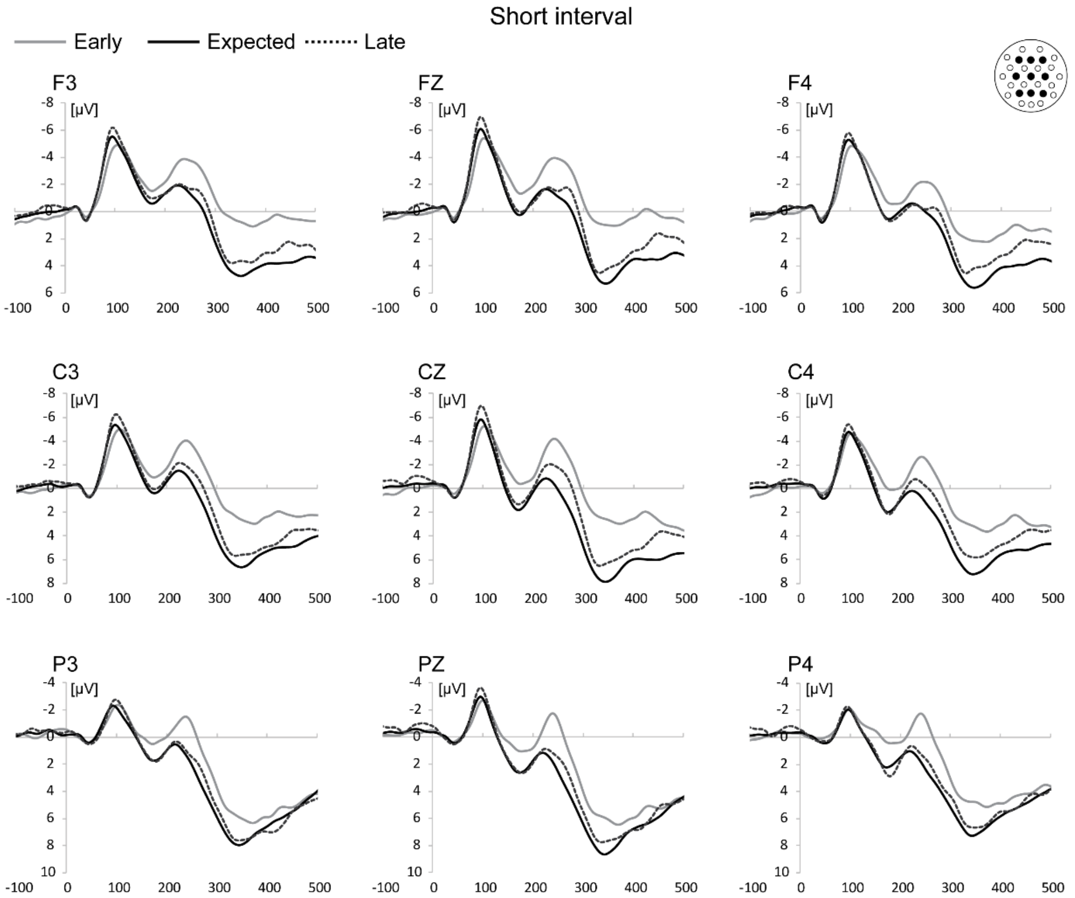


Figure 5.6. Grand average ERPs elicited by target stimuli in the early (gray lines), expected (black lines) and the late foreperiod (dotted lines) during the short interval conditions. The electrode configuration is shown on right top, with the presented electrodes marked black. All tracings are aligned with respect to a 0-50 ms baseline. Negativity is up.

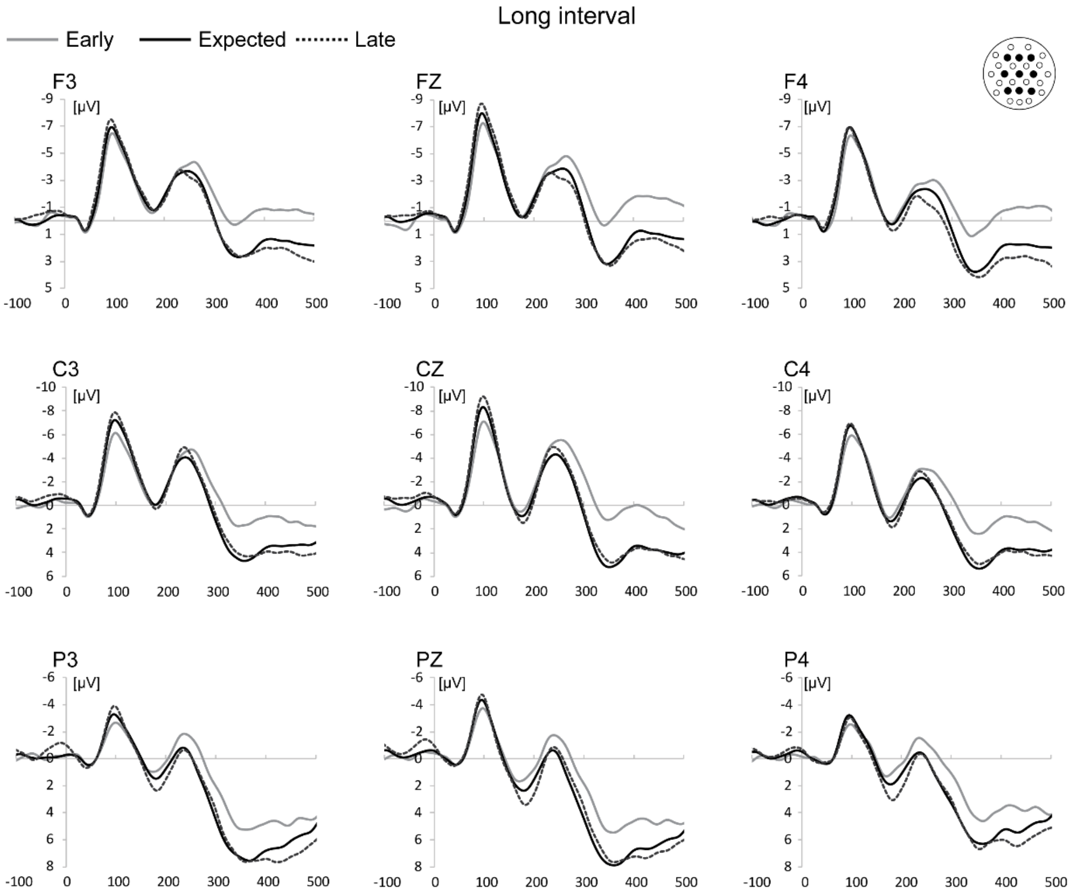


Figure 5.7. Grand average ERPs elicited by target stimuli in the early (gray lines), expected (black lines) and the late foreperiod (dotted lines) during the long interval conditions. The electrode configuration is shown on right top, with the presented electrodes marked black. All tracings are aligned with respect to a 0-50 ms baseline. Negativity is up.

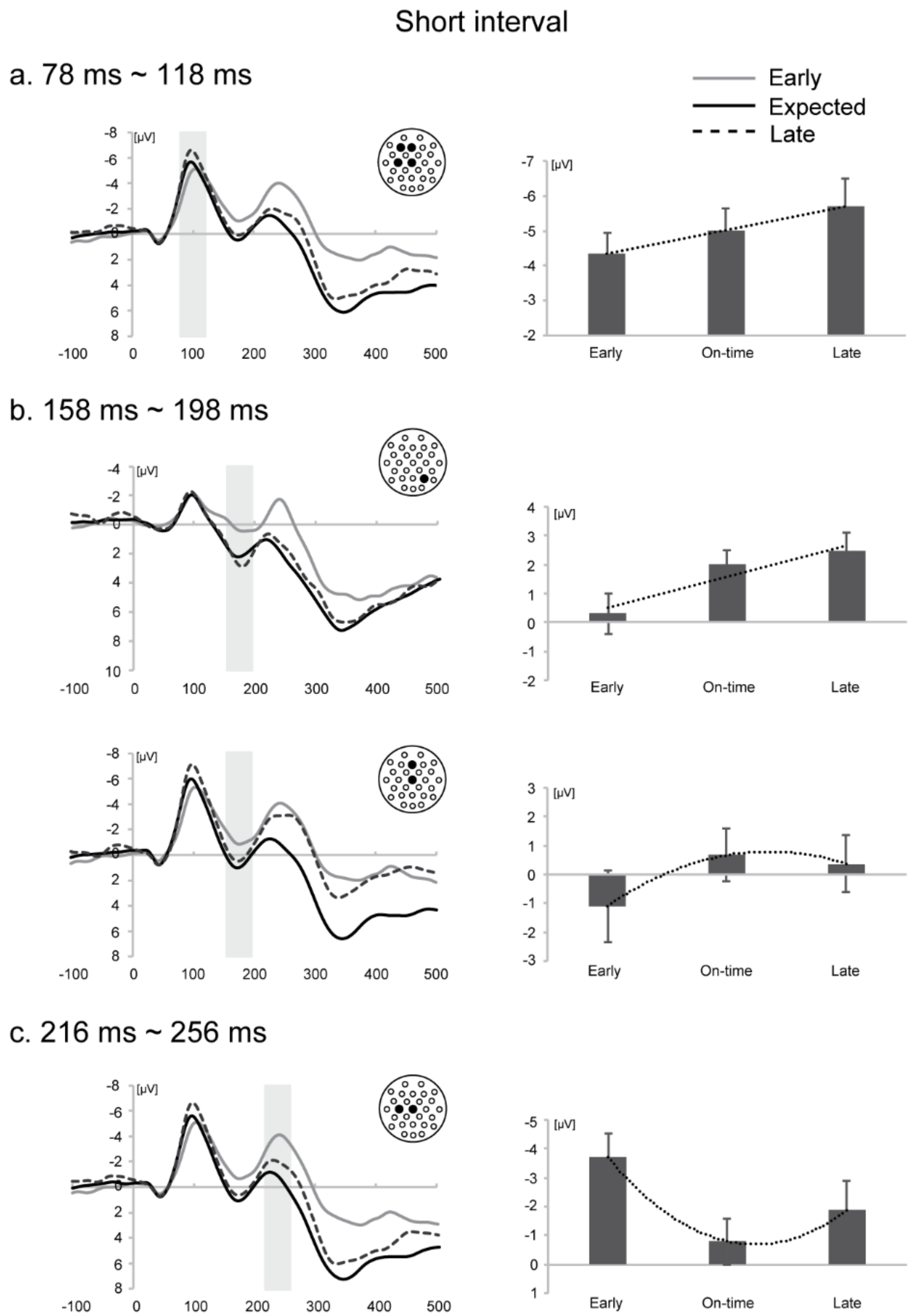


Figure 5.8. Grand average ERPs elicited by target stimuli in the early (gray lines), expected (black lines) and the late foreperiod (dotted lines) during the short interval conditions. a. Over F3, Fz, C3, Cz electrodes, there was a linear effect of foreperiod in

the 78-118 ms time range. b. In the 158 – 198 ms time range, there was a linear effect of foreperiod at the P4 electrode and a quadratic effect of foreperiod over Fz and Cz electrodes. c. Over the C3 and Cz electrodes, there was a quadratic effect of foreperiod in the 216 – 256 ms time range. All tracings are aligned with respect to a 0-50 ms baseline. Error bars are standard error of the mean and y-axes show amplitudes of ERPs in microvolt (μV).

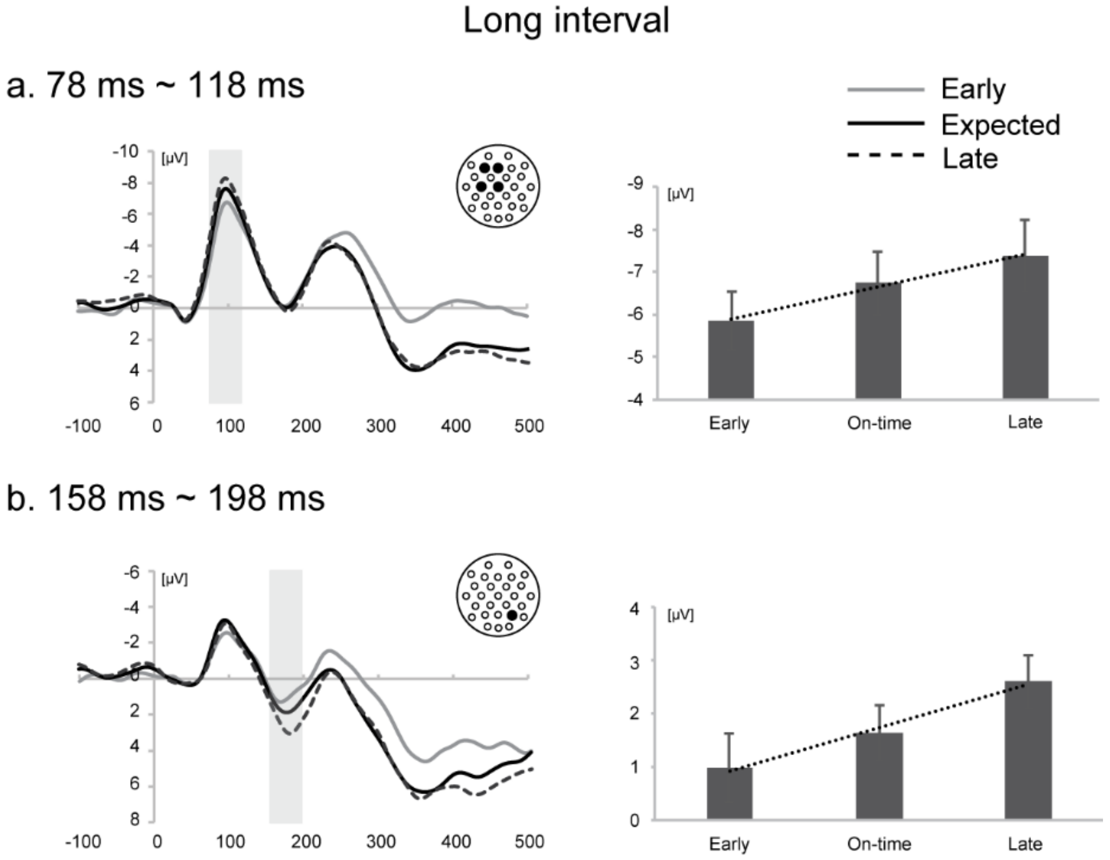


Figure 5.9. Grand average ERPs elicited by target stimuli in the early (gray lines), expected (black lines) and the late foreperiod (dotted lines) during the short interval conditions. a. Over F3, Fz, C3, Cz electrodes, there was a linear effect of foreperiod in the 78-118 ms time range. b. In the 158 – 198 ms time range, there was a linear effect of foreperiod at the P4 electrode. All tracings are aligned with respect to a 0-50 ms baseline. Error bars are standard error of the mean and y-axes show amplitudes of ERPs in microvolt (μV).

5.4 Discussion

Behavioural results with faster RT at the expected moment compared to early and late foreperiod, confirmed our previous founding of U-shaped expectancy profile for both rhythm-based and symbolic cued temporal expectation (Figure 5.2). Moreover, the asymmetric U-shaped curve seem to provide the evidence that both temporal orienting effect (symbolic cued) and foreperiod effect were observed in this temporal expectation processing. In addition, faster RT during the short interval than the long interval, also consistent with our previous studies.

In the N1 time range, there was a main effect of interval with a larger N1 in the short compared to the long interval condition (Figure 5.4). It has been repeatedly shown that the auditory N1 is enhanced for sounds presented at an attended time point [114, 116-118]. The current results may reflect the increase attention focusing at the shorter interval expectation, verified our behavioral results with faster RT during the short compared to long interval condition. Furthermore, in the N1 time range, there was also evidence of a process relating to the foreperiod effect, with a linear increase in amplitude from early to late foreperiod. This effect was presented over left frontal and central regions, during both short and long interval condition, consist with the earlier studies reported an enhanced auditory N1 with increasing interstimulus interval [119-121], Moreover, previous studies proposed a linear increase of N1 amplitudes from early to late stimuli restricted to the left hemisphere, related to the recovery of the N1 with elapsing time, reflect the constant updating temporal expectation online with the passage of time, associated with the foreperiod effect, we confirmed these proposition [120, 122].

Temporal orienting effect was not observed in the N1 time range (Figure 5.8), in accordance with the previous founding, that the enhanced N1 could be only observed in filter paradigms (only attended stimuli require a response), rather than probabilistic cuing paradigms (both attended and unattended stimuli require a response). As in the probabilistic cuing paradigms, the participants had to divide attention between cued expected and unexpected moment, however, filter tasks allowed for a strict focusing of attention to the cued time point. Thus, difference in attention to the cued compared to uncued moment was larger in the filter paradigms, has been suggested result in earlier processing levels affected [123, 124]. Although in earlier studies reported larger effects of temporal orienting when temporal expectation was manipulated between blocks [21], further observed a modulation of N1 processing even in probabilistic cuing paradigms [101], however, in our present study, 60% expected trials, 40% unexpected trial, a less pronounced bias toward the expected moment compared to the earlier studies, may result in no modulation of the early processing.

In the following P2 time range the foreperiod effect was observed at right posterior area during both short and long interval conditions (Figure 5.8 and Figure 5.9). Moreover, Temporal orienting effect was also observed as a U-shaped pattern with enhanced P2 for expected compared to early or late foreperiod at frontal and central areas during short interval conditions. Only a few studies explored the temporal orienting effects on the auditory P2. The present study confirms these latter results. There have only been a few studies explored temporal orienting and foreperiod effect on the P2 component. Alexander Jones et al., found temporal expectancy effect with U-shaped pattern results that smaller P2 for synchronic target to out of synchrony target at posterior areas, also found foreperiod effect with linear increased amplitude from early to late target at central and posterior electrodes [125]. On the contrary Sanabria et al., found an enhanced P2 for synchrony compared to out of synchrony target [79]. The present study confirms the latter results.

The main effect of interval with a larger N2 in the short compared to long interval was also observed at the N2 time range (Figure 5.8). Temporal orienting effect was also observed as a U-shaped pattern with a smaller N2 in the expected compared to early or later foreperiod at the left-central areas during short interval conditions. Consist with the previous studies showed invalid targets elicited larger N2, which linked to a response inhibition process[90]. Griffin et al., 2002 (experiment 2) replicated the previous founding with enhanced N2 at the unattended target [113]. The analogous findings were also observed in the following serious studies [9, 101], with smaller N2 in valid relative to invalid early trials, considered as reflecting conflict detection [126-129]. In this process, conflict detection between the expected and the actual target appearance moment, a reconfiguration of the system was followed to adapt performance to the unexpected situation. Thus, N2 enhanced by a sudden target occur at unexpected moment; N2 attenuated by expected target, which could prevent conflict detection. In addition, the distribution of the N2 effect in the present study was central, as opposed to the posterior distribution for the attended target [113], and anterior negative potentials in the Go/No go task, which participants have to respond to “Go” target and inhibit responses to “No go” target [128]. This suggests that different neural processes are active in these situations, and the functional significance of this N2 effect still awaits clarification.

5.5 Conclusion

Behavioural results observed both temporal orienting and foreperiod effect, with faster responses at the expected and late compared to early foreperiod, but no difference between expected and late foreperiod during both short and long interval conditions. Crucially, ERPs showed evidence of two distinct temporal expectation processes, as the two forms of temporal expectation seem to affect different stages of stimulus processing, foreperiod effect affects processing earlier than the expectation based on symbolic cues. Furthermore, this study shows that temporal expectation driven by symbolic cues and passage of time can work in parallel with distinguishable neural signatures.

Chapter 6 General conclusion and future projections

6.1 General conclusions

The current thesis includes four experiment studies. The first experiment is a leading of the thesis, investigating different neural mechanisms underlying temporal expectation driven by fast and slow rhythm by fMRI. The second experiment evaluate the effect of ISI length on temporal expectancy profiles for rhythm-based temporal expectation. The third experiment, further examined whether temporal expectation driven by rhythmic cues differ from that driven by symbolic cues, based on the behavioural data, the distinction was found between the two forms of temporal expectations. In the results of experiment 2 and 3, we found the temporal expectation driven by rhythmic cues and symbolic cues could be further updating by the passage of time. In the fourth experiment, we investigated the relationships between the temporal expectation driven by symbolic cues and the passage of time by ERP, examined whether they can work in parallel and have distinguishable neural signature.

Chapter 2 Direct comparison of fast rhythm manipulated according to a brief 500 ms inter-stimulus interval (ISI), and slow rhythm with a long 1700ms ms ISI, showed significantly greater activity of left hemisphere insula and left middle frontal gyrus (MFG) when temporal expectation driven by fast rhythm, but bilateral middle temporal gyrus (MTG), Superior frontal gyrus (SFG), left inferior temporal gyrus (ITG), and right caudate were more active when temporal expectation driven by slow rhythm. Revealed distinct neural mechanisms of fast and slow rhythmic temporal expectations.

Chapter 3 verified a U-shaped TEPs for the rhythm-based temporal expectation task.

These TEPs were asymmetrical during the 500 ms and 1500 ms ISI conditions and gradually became symmetrical as the ISI became longer. These results indicated that although regular rhythms generated the temporal expectation effect creating a U-shaped TEP, the temporal expectations were further updated as time passed, which is known as the hazard function, leading to asymmetry. Moreover, the effect of the hazard function seemed to be attenuated as ISI increased. In addition, RT was also progressively slower with the increased ISI, suggesting that rhythm perception is limited; as ISI increased, rhythmic organization tended to collapse and could not predict upcoming event onset time, resulting in less stable synchronization performance.

Chapter 4 verified U-shaped TEPs for both rhythmic and symbolic cued temporal expectation tasks. Moreover, by directly compared rhythmic and symbolic cued temporal expectation by means of a single experimental design. The results showed larger cueing effects for rhythmic cued task compared to symbolic cued task at the short standard interval, indicating that rhythmic cues more reliable and effective in optimizing behavioral performance. Crucially, no difference was found between the two forms of temporal expectation during the long interval, revealing that the behavioral differences between temporal expectations triggered by rhythmic and symbolic cues were likely to diminish as the time interval increased. Overall, we propose that it is difficult to affirm whether temporal expectations driven by rhythmic and symbolic cues have the same or different mechanisms, the distinction between the two forms of temporal expectation will change with timescales.

Chapter 5 Described the relationship between temporal expectation driven by symbolic cues and the passage of time. The behavioural results observed both temporal orienting and foreperiod effect, with faster responses at the expected and late compared to early foreperiod, but no difference between expected and late foreperiod during both short and long interval conditions. Crucially, ERPs showed evidence of two distinct temporal expectation processes, as the two forms of temporal expectation seem to affect different stages of stimulus processing, foreperiod effect affects processing earlier than the expectation based on symbolic cues. Furthermore, the results suggested that temporal expectation driven by symbolic cues and passage of time can work in parallel with distinguishable neural signatures.

6.2 Future projections

Firstly, the current results of the thesis the results showed foreperiod effect, but no temporal orienting effect observed in the N1 time range, revealed that temporal expectation driven by passage of time processing earlier than the expectation based on symbolic cues. One conceivable assumption is that a less pronounced bias toward the expected moment (60%) may result in no modulation of the early processing. Therefore, one of the important challenges for the future studies is investigating the effect of expected probability on the stages of stimulus processing affect by the two forms of temporal expectation.

Additionally, the current studies examined the neural mechanisms underlying three kinds of temporal expectation across millisecond to second time scale limited to young adults, future studies will focus on development trajectory of temporal expectation across the life span to uncover the neural mechanism underlying different types of temporal expectations. Additionally, another important challenge is to extent the current study to special populations (e.g. patients with Mild cognitive impairment, and Alzheimer's disease) to provide important basis for the early clinical detection and rehabilitation of special brain disease.

Appendix

Simple Introduction of EEG Apparatus

The BrainAmp MR plus was manufactured by BrainProduct Inc., Germany. This amplifier is a compact solution for neurophysiology research that can be combined with other units within the same product family to cover a vast range of possible application areas. This fully portable solution can be used for standard EEG/ERP recordings and can also be placed inside of the MRI bore for simultaneous EEG/fMRI acquisitions (Figure A1).

Thanks to its 5 kHz sampling rate per channel, the BrainAmp can be used to record EEG, EOG, and EMG signals as well as evoked potentials with a frequency up to 1 kHz. The 16-bit TTL trigger input allows the detection of a large number of markers from visual, acoustic, electrical, magnetic or other stimulation modalities. The BrainAmps can be used both with passive and active electrodes offering a great degree of flexibility.

The 32 channel units can be stacked to expand the number of channels up to 256 and combined with the BrainAmp ExG to record EEG, EOG, EMG, ECG, GSR (Galvanic Skin Response) and many other types of bipolar and auxiliary signals.

Figure A1. EEG amplifier of BrainAmp MR plus

Table A1. Technical specifications of BrainAmp MR plus

Number of Channels per unit	32
Max. Number of channels	128
Reference Type	unipolar
MR-compatibility	Yes (for scanners up to 4 Tesla)
Bandwidth [Hz]	DC - 1000
High Pass Filter [Hz]	0.016 / 10 s AC or DC switchable
Low Pass Filter [Hz]	1000 / 250 switchable
Input Noise [µVpp]	≤ 1
Input Impedance [MΩ]	10 / 10000
Input Measurement Ground / eference	Yes
A/D-C [bit]	16
A/D-Rate [Hz]	5000
Max. Sampling Frequency [Hz]	5000
Offset Compatibility [mV]	± 300
Operating Range [mV]	selectable: ±3.2768; ±16.384; ±327.68
Resolution [µV]	selectable: 0.1; 0.5; 10.0
CMRR [dB]	≥ 110
TTL Trigger Input [bit]	16
Synchronized Digital Trigger Input [bit]	up to 16
Max. Power Consumption [mA]	160
Power Supply	rechargeable Battery
Signal Transmission	optical
PC Interface	PCI, USB 2.0
Deblocking Function	Yes
Blocking of Unused Channels	Yes
Safety	Twin Fiber optical Transmission Protection Class II, Type BF IEC EN 60601 EMC tested, electrically safe
Classification to MDD 93/42/EEC	Class IIa
Dimensions H x W x D [mm]	68 x 160 x 187
Weight [kg]	1.1

The current thesis adapted 32 electrodes of this apparatus. The location and name of each channel that the present study was used is displayed in Figure A2.

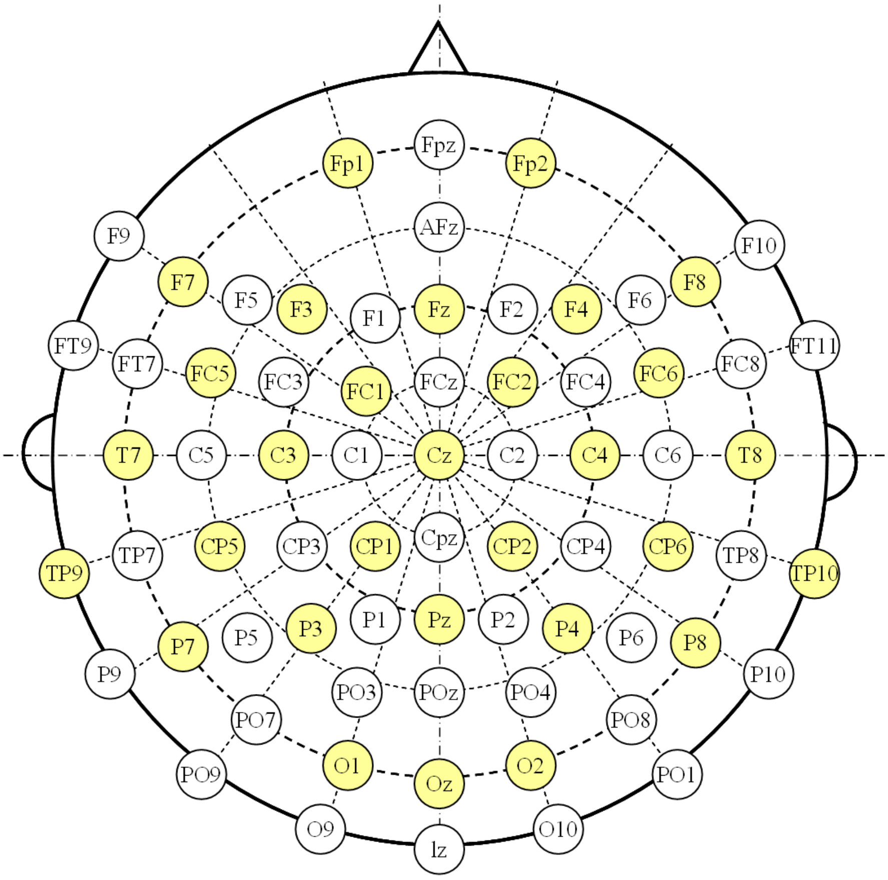


Figure A2. The locations and names of each electrode.

Publications

Journal Papers

[1] Effects of interstimulus interval length on rhythm-based temporal expectation.
Zhihan Xu, Yanna Ren, Yoshimichi Ejima, Jiajia Yang, Satoshi Takahashi, Qiong Wu, Jinglong Wu.
Information, Vol. 21, No. 12, (2019).

[2] Effect of Aging on the Human Kinetic Visual Field.
Satoshi Takahashi, ***Zhihan Xu***, Masanori Tanida and Jinglong Wu.
Neuroscience and Biomedical Engineering, Volume 4, pp. 50-56 (2016).

[3] Enhancement of Delayed Audiovisual Response in Parkinson’s Disease: A Comparison with Normal Aged Controls.
Qiong Wu, Jiajia Yang, Chunlin Li, Yujie Li, ***Zhihan Xu***, Yoshimichi Ejima, Yasuyuki Ohta, Koji Abe and Jinglong Wu.
Neuroscience and Biomedical Engineering, Volume 4, pp. 125-131, (2016).

[4] Decreased resting-state connections within the visuospatial attention-related network in advanced aging.
Yujie Li, Chunlin Li, Qiong Wu, ***Zhihan Xu***, Tomoko Kurata, Seiichiro Ohno, Susumu Kanazawa, Koji Abef, Jinglong Wu.
Neuroscience Letters, Volume 597, pp. 13-18, (2015).

International Conference Paper

[1] The Expectancy Profile for Rhythm-Based Temporal Prediction.
Zhihan Xu, Qiong Wu, Chunlin Li, Jiajia Yang, Satoshi Takahashi, Yoshimichi Ejima, Jinglong Wu.
International Conference on Complex Medical Engineering (ICME), p. 53, (2017).

[2] A Basic Study for Improving the Predictability of Amber Traffic Lights: Comparing the Brief and Long Interval Rhythm Prediction.
Zhihan Xu, Qiong Wu, Chunlin Li, Yujie Li, Yuta Kataoka, Seiichiro Ohno, Susumu Kanazawa, Satoshi Takahashi, Jinglong Wu.
Proceedings of 2016 IEEE International Conference on Mechatronics and Automation (ICMA), pp. 2587-2592, (2016).

[3] Different Neural Network for Exogenous Temporal Expectations under Sub-second and Supra-second in fMRI.
Zhihan Xu, Qiong Wu, Chunlin Li, Yujie Li, Yuta Kataoka, Seiichiro Ohno,

Susumu Kanazawa, Satoshi Takahashi, Jinglong Wu.
Proceedings of 2014 IEEE International Conference on Mechatronics and Automation (ICMA), pp. 1734-1739, (2014).

[4] An fMRI study on the effect of distance in the shifting of visuospatial attention.
Qiong Wu, Yujie Li, ***Zhihan Xu***, Goshi Miyamoto, Chunlin Li, Oono Seiichiro, Kanazawa Susumu, Jinglong Wu.
Proceedings of 2014 IEEE International Conference on Mechatronics and Automation (ICMA), pp. 221-226, (2014).

Book chapter

[1]. Research on Current Situations for Functional Classification of Timing.
Zhihan Xu, Qiong Wu, Chunlin Li, Yujie Li, Hongbin Han, Dehua Chui, Satoshi Takahashi, Jinglong Wu. Improving the Quality of Life for Dementia Patients through Progressive Detection, Treatment, and Care. Hershey, PA, USA: IGI Global, pp. 222-235, (2017).

Acknowledgements

Firstly, I would like to express my sincerely gratitude to Prof. Jinglong Wu for the continuous support during my Ph.D studies and related researches. Prof. Jinglong Wu helped me in all my research design and writing of this thesis. I could not complete my study of doctor course and finish this thesis successfully without his enlightening instruction, impressive kindness and patience. His diligence gives me power not only during my present PhD scours, but also in my future life. In addition, Prof. Wu also helps me also for my daily life, and let my life in japan much easier.

Secondly, I would lie to express my sincerely gratitude to my supervisor Prof. Satoshi Takahashi. I got a lot of comments for Prof. Satoshi Takahashi during my research plan, conduct my experiments, write published papers and this thesis. During the PhD scours, Prof. Satoshi Takahashi also greatly supports me when I applied the scholarships.

Last but not the least, I would also like to express my sincere thanks to Prof. Yoshimichi Ejima, who provided me a lot of comments during I write my papers. Without their precious support, it would not be possible to conduct this thesis successfully. I express sincere thanks to Assistant Professor Qiong Wu and Jiajia Yang. I thank my fellow lab mates in for the stimulating discussions and for all the fun we have had together during these years. I would like to thank my parents and friends for supporting me spiritually throughout writing this thesis and my life in general.

References

[1] E. W. Large and M. R. Jones, "The dynamics of attending: How people track time-varying events," *Psychological Review,* vol. 106, pp. 119-159, Jan 1999.

[2] J. S. Snyder and E. W. Large, "Gamma-band activity reflects the metric structure of rhythmic tone sequences," *Brain Res Cogn Brain Res,* vol. 24, pp. 117-26, Jun 2005.

[3] J. D. McAuley, "Perception of time as phase: Toward an adaptive-oscillator model of rhythmic pattern processing," 1995.

[4] J. D. McAuley and G. R. Kidd, "Effect of deviations from temporal expectations on tempo discrimination of isochronous tone sequences," *J Exp Psychol Hum Percept Perform,* vol. 24, pp. 1786-800, Dec 1998.

[5] M. R. Jones, H. Moynihan, N. MacKenzie, and J. Puente, "Temporal aspects of stimulus-driven attending in dynamic arrays," *Psychol Sci,* vol. 13, pp. 313-9, Jul 2002.

[6] M. R. Jones, H. M. Johnston, and J. Puente, "Effects of auditory pattern structure on anticipatory and reactive attending," *Cogn Psychol,* vol. 53, pp. 59-96, Aug 2006.

[7] M. R. Jones, "Attending to sound patterns and the role of entrainment," *Attention and time,* pp. 317-330, 2010.

[8] A. M. Cravo, G. Rohenkohl, V. Wyart, and A. C. Nobre, "Temporal expectation enhances contrast sensitivity by phase entrainment of low-frequency oscillations in visual cortex," *J Neurosci,* vol. 33, pp. 4002-10, Feb 27 2013.

[9] J. R. Doherty, A. Rao, M. M. Mesulam, and A. C. Nobre, "Synergistic effect of combined temporal and spatial expectations on visual attention," *J Neurosci,* vol. 25, pp. 8259-66, Sep 7 2005.

[10] G. Rohenkohl, A. M. Cravo, V. Wyart, and A. C. Nobre, "Temporal expectation improves the quality of sensory information," *J Neurosci,* vol. 32, pp. 8424-8428, Jun 13 2012.

[11] D. Sanabria, M. Capizzi, and A. Correa, "Rhythms That Speed You Up," *Journal of Experimental Psychology-Human Perception and Performance,* vol. 37, pp. 236-244, Feb 2011.

[12] T. Martin, R. Egly, J. M. Houck, J. P. Bish, B. D. Barrera, D. C. Lee*, et al.*, "Chronometric evidence for entrained attention," *Percept Psychophys,* vol. 67, pp. 168-84, Jan 2005.

[13] K. E. Mathewson, M. Fabiani, G. Gratton, D. M. Beck, and A. Lleras, "Rescuing

stimuli from invisibility: Inducing a momentary release from visual masking with pre-target entrainment," *Cognition,* vol. 115, pp. 186-91, Apr 2010.

[14] T. Martin, J. M. Houck, J. P. Bish, D. Kicic, C. C. Woodruff, S. N. Moses*, et al.*, "MEG reveals different contributions of somatomotor cortex and cerebellum to simple reaction time after temporally structured cues," *Hum Brain Mapp,* vol. 27, pp. 552-61, Jul 2006.

[15] A. Correa and A. C. Nobre, "Neural modulation by regularity and passage of time," *J Neurophysiol,* vol. 100, pp. 1649-55, Sep 2008.

[16] R. M. Church and H. A. Broadbent, "Alternative representations of time, number, and rate," *Cognition,* vol. 37, pp. 55-81, Nov 1990.

[17] J. Gibbon, "Scalar expectancy theory and Weber's law in animal timing," *Psychological review,* vol. 84, p. 279, 1977.

[18] J. Gibbon, R. M. Church, and W. H. Meck, "Scalar timing in memory," *Ann N Y Acad Sci,* vol. 423, pp. 52-77, 1984.

[19] B. C. Rakitin, J. Gibbon, T. B. Penney, C. Malapani, S. C. Hinton, and W. H. Meck, "Scalar expectancy theory and peak-interval timing in humans," *J Exp Psychol Anim Behav Process,* vol. 24, pp. 15-33, Jan 1998.

[20] M. Treisman, Temporal discrimination and the indifference interval: implications for a model of the "internal clock.". Washington: American Psychological Association, 1963.

[21] A. Correa, J. Lupianez, B. Milliken, and P. Tudela, "Endogenous temporal orienting of attention in detection and discrimination tasks," *Percept Psychophys,* vol. 66, pp. 264-78, Feb 2004.

[22] A. Correa, J. Lupianez, and P. Tudela, "The attentional mechanism of temporal orienting: determinants and attributes," *Exp Brain Res,* vol. 169, pp. 58-68, Feb 2006.

[23] J. T. Coull, C. D. Frith, C. Buchel, and A. C. Nobre, "Orienting attention in time: behavioural and neuroanatomical distinction between exogenous and endogenous shifts," *Neuropsychologia,* vol. 38, pp. 808-819, 2000.

[24] M. Trivino, A. Correa, M. Arnedo, and J. Lupianez, "Temporal orienting deficit after prefrontal damage," *Brain,* vol. 133, pp. 1173-85, Apr 2010.

[25] P. Niemi and R. Näätänen, "Foreperiod and simple reaction time," *Psychological bulletin,* vol. 89, p. 133, 1981.

[26] A. Elithorn and C. Lawrence, "Central inhibition-some refractory observations," *Quarterly Journal of Experimental Psychology,* vol. 7, pp. 116-127, 1955.

[27] R. D. Luce, Response times: Their role in inferring elementary mental organization: Oxford University Press on Demand, 1986.

[28] S. A. Los, "Foreperiod and sequential effects: theory and data," *Attention and time,* vol. 289, p. 24, 2010.

[29] A. Vallesi, "Neuro-anatomical substrates of foreperiod effects," *Attention and time,* pp. 303-316, 2010.

[30] L. Karlin, "Reaction time as a function of foreperiod duration and variability," *Journal of Experimental Psychology,* vol. 58, p. 185, 1959.

[31] G. Mento, V. Tarantino, A. Vallesi, and P. S. Bisiacchi, "Spatiotemporal neurodynamics underlying internally and externally driven temporal prediction: a high spatial resolution ERP study," *J Cogn Neurosci,* vol. 27, pp. 425-39, Mar 2015.

[32] J. T. Coull, "Neural substrates of mounting temporal expectation," *PLoS Biol,* vol. 7, p. e1000166, Aug 2009.

[33] A. C. Nobrel, A. Correa, and J. T. Coull, "The hazards of time," *Current Opinion in Neurobiology,* vol. 17, pp. 465-470, Aug 2007.

[34] J. T. Coull, "Discrete neuroanatomical substrates for generating and updating temporal expectations," in *Space, Time and Number in the Brain*, ed: Elsevier, 2011, pp. 87-101.

[35] D. T. Stuss, M. P. Alexander, T. Shallice, T. W. Picton, M. A. Binns, R. Macdonald*, et al.*, "Multiple frontal systems controlling response speed," *Neuropsychologia,* vol. 43, pp. 396-417, 2005.

[36] A. Vallesi, A. Mussoni, M. Mondani, R. Budai, M. Skrap, and T. Shallice, "The neural basis of temporal preparation: Insights from brain tumor patients," *Neuropsychologia,* vol. 45, pp. 2755-63, Sep 20 2007.

[37] A. Vallesi, A. R. McIntosh, T. Shallice, and D. T. Stuss, "When Time Shapes Behavior: fMRI Evidence of Brain Correlates of Temporal Monitoring," *Journal of Cognitive Neuroscience,* vol. 21, pp. 1116-1126, Jun 2009.

[38] A. Vallesi, A. R. McIntosh, and D. T. Stuss, "Temporal preparation in aging: a functional MRI study," *Neuropsychologia,* vol. 47, pp. 2876-81, Nov 2009.

[39] D. Bueti, B. Bahrami, V. Walsh, and G. Rees, "Encoding of temporal probabilities in the human brain," *J Neurosci,* vol. 30, pp. 4343-52, Mar 24 2010.

[40] J. Coull and A. Nobre, "Dissociating explicit timing from temporal expectation with fMRI," *Curr Opin Neurobiol,* vol. 18, pp. 137-44, Apr 2008.

[41] R. Barnes and M. R. Jones, "Expectancy, attention, and time," *Cognitive Psychology,* vol. 41, pp. 254-311, Nov 2000.

[42] S. A. Los and D. J. Heslenfeld, "Intentional and unintentional contributions to nonspecific preparation: electrophysiological evidence," *J Exp Psychol Gen,* vol. 134, pp. 52-72, Feb 2005.

[43] S. A. Los and C. E. van den Heuvel, "Intentional and unintentional contributions

to nonspecific preparation during reaction time foreperiods," *J Exp Psychol Hum Percept Perform,* vol. 27, pp. 370-86, Apr 2001.

[44] A. Vallesi and C. Crescentini, "Right fronto-parietal involvement in monitoring spatial trajectories," *Neuroimage,* vol. 57, pp. 558-64, Jul 15 2011.

[45] J. A. Grahn, "Neural mechanisms of rhythm perception: current findings and future perspectives," *Top Cogn Sci,* vol. 4, pp. 585-606, Oct 2012.

[46] R. B. Ivry and J. E. Schlerf, "Dedicated and intrinsic models of time perception," *Trends Cogn Sci,* vol. 12, pp. 273-80, Jul 2008.

[47] G. Koch, M. Oliveri, S. Torriero, S. Salerno, E. Lo Gerfo, and C. Caltagirone, "Repetitive TMS of cerebellum interferes with millisecond time processing," *Exp Brain Res,* vol. 179, pp. 291-9, May 2007.

[48] P. A. Lewis and R. C. Miall, "Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging," *Curr Opin Neurobiol,* vol. 13, pp. 250-5, Apr 2003.

[49] T. H. Rammsayer, "The effects of type of interval, sensory modality, base duration, and psychophysical task on the discrimination of brief time intervals," *Atten Percept Psychophys,* vol. 76, pp. 1185-96, May 2014.

[50] J. A. Michon, "The compleat time experiencer," in *Time, mind, and behavior*, ed: Springer, 1985, pp. 20-52.

[51] T. H. Rammsayer, "Differences in duration discrimination of filled and empty auditory intervals as a function of base duration," *Atten Percept Psychophys,* vol. 72, pp. 1591-600, Aug 2010.

[52] T. Rammsayer and R. Ulrich, "Elaborative rehearsal of nontemporal information interferes with temporal processing of durations in the range of seconds but not milliseconds," *Acta Psychol (Amst),* vol. 137, pp. 127-33, May 2011.

[53] M. J. Hayashi, M. Kantele, V. Walsh, S. Carlson, and R. Kanai, "Dissociable neuroanatomical correlates of subsecond and suprasecond time perception," *Journal of Cognitive Neuroscience,* vol. 26, pp. 1685-1693, 2014.

[54] A. C. Livesey, M. B. Wall, and A. T. Smith, "Time perception: manipulation of task difficulty dissociates clock functions from other cognitive demands," *Neuropsychologia,* vol. 45, pp. 321-31, Jan 28 2007.

[55] D. Bueti and E. Macaluso, "Physiological correlates of subjective time: evidence for the temporal accumulator hypothesis," *Neuroimage,* vol. 57, pp. 1251-63, Aug 1 2011.

[56] J. T. Coull, K. Davranche, B. Nazarian, and F. Vidal, "Functional anatomy of timing differs for production versus prediction of time intervals," *Neuropsychologia,* vol. 51, pp. 309-19, Jan 2013.

[57] R. S. Sutton and A. G. Barto, "Toward a modern theory of adaptive networks: expectation and prediction," *Psychol Rev,* vol. 88, pp. 135-70, Mar 1981.

[58] N. U. Dosenbach, K. M. Visscher, E. D. Palmer, F. M. Miezin, K. K. Wenger, H. C. Kang*, et al.*, "A core system for the implementation of task sets," *Neuron,* vol. 50, pp. 799-812, Jun 1 2006.

[59] V. Menon and L. Q. Uddin, "Saliency, switching, attention and control: a network model of insula function," *Brain Struct Funct,* vol. 214, pp. 655-67, Jun 2010.

[60] M. Wittmann, A. N. Simmons, J. L. Aron, and M. P. Paulus, "Accumulation of neural activity in the posterior insula encodes the passage of time," *Neuropsychologia,* vol. 48, pp. 3110-20, Aug 2010.

[61] F. du Boisgueheneuc, R. Levy, E. Volle, M. Seassau, H. Duffau, S. Kinkingnehun*, et al.*, "Functions of the left superior frontal gyrus in humans: a lesion study," *Brain,* vol. 129, pp. 3315-28, Dec 2006.

[62] W. H. Meck, "Neuropharmacology of timing and time perception," *Brain Res Cogn Brain Res,* vol. 6, p. 233, Jan 1998.

[63] D. L. Harrington, K. Y. Haaland, and N. Hermanowicz, "Temporal processing in the basal ganglia," *Neuropsychology,* vol. 12, pp. 3-12, Jan 1998.

[64] C. Malapani, B. Rakitin, R. Levy, W. H. Meck, B. Deweer, B. Dubois*, et al.*, "Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction," *J Cogn Neurosci,* vol. 10, pp. 316-31, May 1998.

[65] M. R. Jones, H. M. Johnston, and J. Puente, "Effects of auditory pattern structure on anticipatory and reactive attending," *Cognitive Psychology,* vol. 53, pp. 59-96, Aug 2006.

[66] S. Grondin, "Timing and time perception: a review of recent behavioral and neuroscience findings and theoretical directions," *Attention, Perception, & Psychophysics,* vol. 72, pp. 561-582, 2010.

[67] R. B. Ivry and J. E. Schlerf, "Dedicated and intrinsic models of time perception," *Trends in Cognitive Sciences,* vol. 12, pp. 273-280, Jul 2008.

[68] A. C. Nobre, "Orienting attention to instants in time," *Neuropsychologia,* vol. 39, pp. 1317-28, 2001.

[69] H. Merchant, W. Zarco, and L. Prado, "Do we have a common mechanism for measuring time in the hundreds of millisecond range? Evidence from multiple-interval timing tasks," *Journal of Neurophysiology,* vol. 99, pp. 939-949, Feb 2008.

[70] H. N. Zelaznik, R. M. Spencer, and R. B. Ivry, "Dissociation of explicit and implicit timing in repetitive tapping and drawing movements," *J Exp Psychol Hum Percept Perform,* vol. 28, pp. 575-88, Jun 2002.

[71] H. N. Zelaznik, R. M. Spencer, R. B. Ivry, A. Baria, M. Bloom, L. Dolansky*, et al.*, "Timing variability in circle drawing and tapping: probing the relationship between event and emergent timing," *J Mot Behav,* vol. 37, pp. 395-403, Sep 2005.

[72] F. Macar and F. Vidal, "The CNV peak: an index of decision making and temporal memory," *Psychophysiology,* vol. 40, pp. 950-954, 2003.

[73] M. Pfeuty, R. Ragot, and V. Pouthas, "When time is up: CNV time course differentiates the roles of the hemispheres in the discrimination of short tone durations," *Experimental Brain Research,* vol. 151, pp. 372-379, 2003.

[74] P. Praamstra, D. Kourtis, H. F. Kwok, and R. Oostenveld, "Neurophysiology of implicit timing in serial choice reaction-time performance," *Journal of Neuroscience,* vol. 26, pp. 5448-5455, 2006.

[75] M. Wiener, P. Turkeltaub, and H. B. Coslett, "The image of time: a voxel-wise meta-analysis," *Neuroimage,* vol. 49, pp. 1728-1740, 2010.

[76] M. Wiener, P. E. Turkeltaub, and H. B. Coslett, "Implicit timing activates the left inferior parietal cortex," *Neuropsychologia,* vol. 48, pp. 3967-3971, 2010.

[77] S. Vangkilde, A. Petersen, and C. Bundesen, "Temporal expectancy in the context of a theory of visual attention," *Philos Trans R Soc Lond B Biol Sci,* vol. 368, p. 20130054, Oct 19 2013.

[78] J. T. Coull, J. Cotti, and F. Vidal, "Differential roles for parietal and frontal cortices in fixed versus evolving temporal expectations: Dissociating prior from posterior temporal probabilities with fMRI," *Neuroimage,* vol. 141, pp. 40-51, Nov 1 2016.

[79] D. Sanabria and A. Correa, "Electrophysiological evidence of temporal preparation driven by rhythms in audition," *Biological Psychology,* vol. 92, pp. 98-105, Feb 2013.

[80] F. Piras and J. T. Coull, "Implicit, Predictive Timing Draws upon the Same Scalar Representation of Time as Explicit Timing," *Plos One,* vol. 6, Mar 25 2011.

[81] S. Droit-Volet and J. T. Coull, "Distinct developmental trajectories for explicit and implicit timing," *Journal of Experimental Child Psychology,* vol. 150, pp. 141-154, Oct 2016.

[82] J. T. Coull and A. C. Nobre, "Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI," *J Neurosci,* vol. 18, pp. 7426-35, Sep 15 1998.

[83] A. C. Nobre, "Orienting attention to instants in time," *Neuropsychologia,* vol. 39, pp. 1317-1328, 2001.

[84] A. Correa, J. Lupianez, and P. Tudela, "Attentional preparation based on

temporal expectancy modulates processing at the perceptual level," *Psychonomic Bulletin & Review,* vol. 12, pp. 328-334, Apr 2005.

[85] K. Davranche, B. Nazarian, F. Vidal, and J. Coull, "Orienting Attention in Time Activates Left Intraparietal Sulcus for Both Perceptual and Motor Task Goals," *Journal of Cognitive Neuroscience,* vol. 23, pp. 3318-3330, Nov 2011.

[86] I. C. Griffin, C. Miniussi, and A. C. Nobre, "Orienting attention in time," *Frontiers in Bioscience,* vol. 6, pp. D660-D671, Apr 2001.

[87] G. Rohenkohl, J. T. Coull, and A. C. Nobre, "Behavioural Dissociation between Exogenous and Endogenous Temporal Orienting of Attention," *Plos One,* vol. 6, Jan 28 2011.

[88] A. Breska and L. Y. Deouell, "Automatic Bias of Temporal Expectations following Temporally Regular Input Independently of High-level Temporal Expectation," *Journal of Cognitive Neuroscience,* vol. 26, pp. 1555-1571, Jul 2014.

[89] M. D. de la Rosa, D. Sanabria, M. Capizzi, and A. Correa, "Temporal Preparation Driven by Rhythms is Resistant to Working Memory Interference," *Front Psychol,* vol. 3, p. 308, 2012.

[90] C. Miniussi, E. L. Wilding, J. T. Coull, and A. C. Nobre, "Orienting attention in time - Modulation of brain potentials," *Brain,* vol. 122, pp. 1507-1518, Aug 1999.

[91] M. Capizzi, D. Sanabria, and A. Correa, "Dissociating controlled from automatic processing in temporal preparation," *Cognition,* vol. 123, pp. 293-302, May 2012.

[92] M. Schwartze, K. Rothermich, M. Schmidt-Kassow, and S. A. Kotz, "Temporal regularity effects on pre-attentive and attentive processing of deviance," *Biol Psychol,* vol. 87, pp. 146-51, Apr 2011.

[93] G. Rohenkohl and A. C. Nobre, "Alpha Oscillations Related to Anticipatory Attention Follow Temporal Expectations," *Journal of Neuroscience,* vol. 31, pp. 14076-14084, Oct 5 2011.

[94] M. Trivino, M. Arnedo, J. Lupianez, J. Chirivella, and A. Correa, "Rhythms can overcome temporal orienting deficit after right frontal damage," *Neuropsychologia,* vol. 49, pp. 3917-3930, Dec 2011.

[95] J. E. Miller, L. A. Carlson, and J. D. McAuley, "When What You Hear Influences When You See: Listening to an Auditory Rhythm Influences the Temporal Allocation of Visual Attention," *Psychological Science,* vol. 24, pp. 11-18, Jan 2013.

[96] A. Jones, "Independent effects of bottom-up temporal expectancy and top-down spatial attention. An audiovisual study using rhythmic cueing," *Frontiers in*

Integrative Neuroscience, vol. 8, Jan 6 2015.

[97] P. Fraisse, "Rhythm and tempo," *The psychology of music,* vol. 1, pp. 149-180, 1982.

[98] E. Szelag, N. von Steinbuchel, M. Reiser, E. Gilles de Langen, and E. Poppel, "Temporal constraints in processing of nonverbal rhythmic patterns," *Acta Neurobiol Exp (Wars),* vol. 56, pp. 215-25, 1996.

[99] E. Poppel, "A hierarchical model of temporal perception," *Trends Cogn Sci,* vol. 1, pp. 56-61, May 1997.

[100] M. I. Posner, C. R. Snyder, and B. J. Davidson, "Attention and the detection of signals," *J Exp Psychol,* vol. 109, pp. 160-74, Jun 1980.

[101] A. Correa, J. Lupianez, E. Madrid, and P. Tudela, "Temporal attention enhances early visual processing: a review and new evidence from event-related potentials," *Brain Res,* vol. 1076, pp. 116-28, Mar 3 2006.

[102] J. T. Coull, "fMRI studies of temporal attention: allocating attention within, or towards, time," *Brain Res Cogn Brain Res,* vol. 21, pp. 216-26, Oct 2004.

[103] D. Drazin, "Effects of foreperiod, foreperiod variability, and probability of stimulus occurrence on simple reaction time," *Journal of Experimental Psychology,* vol. 62, p. 43, 1961.

[104] X. Cui, C. Stetson, P. R. Montague, and D. M. Eagleman, "Ready...go: Amplitude of the FMRI signal encodes expectation of cue arrival time," *PLoS Biol,* vol. 7, p. e1000167, Aug 2009.

[105] J. Cotti, G. Rohenkohl, M. Stokes, A. C. Nobre, and J. T. Coull, "Functionally dissociating temporal and motor components of response preparation in left intraparietal sulcus," *Neuroimage,* vol. 54, pp. 1221-30, Jan 15 2011.

[106] D. T. Field and J. P. Wann, "Perceiving time to collision activates the sensorimotor cortex," *Curr Biol,* vol. 15, pp. 453-8, Mar 8 2005.

[107] F. Macar, J. Coull, and F. Vidal, "The supplementary motor area in motor and perceptual time processing: fMRI studies," *Cogn Process,* vol. 7, pp. 89-94, Jun 2006.

[108] M. Wiener, P. Turkeltaub, and H. B. Coslett, "The image of time: a voxel-wise meta-analysis," *Neuroimage,* vol. 49, pp. 1728-40, Jan 15 2010.

[109] A. Bischoff-Grethe, M. Martin, H. Mao, and G. S. Berns, "The context of uncertainty modulates the subcortical response to predictability," *J Cogn Neurosci,* vol. 13, pp. 986-93, Oct 1 2001.

[110] R. N. Henson, T. Shallice, and R. J. Dolan, "Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis," *Brain,* vol. 122 (Pt 7), pp. 1367-81, Jul 1999.

[111] A. Vallesi, A. R. McIntosh, T. Shallice, and D. T. Stuss, "When time shapes

behavior: fMRI evidence of brain correlates of temporal monitoring," *J Cogn Neurosci,* vol. 21, pp. 1116-26, Jun 2009.

[112] A. Vallesi, T. Shallice, and V. Walsh, "Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation," *Cereb Cortex,* vol. 17, pp. 466-74, Feb 2007.

[113] I. C. Griffin, C. Miniussi, and A. C. Nobre, "Multiple mechanisms of selective attention: differential modulation of stimulus processing by attention to space or time," *Neuropsychologia,* vol. 40, pp. 2325-40, 2002.

[114] K. Lange, "The N1 effect of temporal attention is independent of sound location and intensity: implications for possible mechanisms of temporal attention," *Psychophysiology,* vol. 49, pp. 1468-80, Nov 2012.

[115] K. Lange, U. M. Kramer, and B. Roder, "Attending points in time and space," *Exp Brain Res,* vol. 173, pp. 130-40, Aug 2006.

[116] L. D. Sanders and L. B. Astheimer, "Temporally selective attention modulates early perceptual processing: event-related potential evidence," *Percept Psychophys,* vol. 70, pp. 732-42, May 2008.

[117] K. Lange and B. Roder, "Orienting attention to points in time improves stimulus processing both within and across modalities," *Journal of Cognitive Neuroscience,* vol. 18, pp. 715-729, May 2006.

[118] K. Lange, F. Rosler, and B. Roder, "Early processing stages are modulated when auditory stimuli are presented at an attended moment in time: an event-related potential study," *Psychophysiology,* vol. 40, pp. 806-17, Sep 2003.

[119] H. Davis, T. Mast, N. Yoshie, and S. Zerlin, "The slow response of the human cortex to auditory stimuli: recovery process," *Electroencephalography and clinical neurophysiology,* vol. 21, pp. 105-113, 1966.

[120] R. Hari, K. Kaila, T. Katila, T. Tuomisto, and T. Varpula, "Interstimulus interval dependence of the auditory vertex response and its magnetic counterpart: implications for their neural generation," *Electroencephalography and clinical neurophysiology,* vol. 54, pp. 561-569, 1982.

[121] R. Näätänen and T. Picton, "The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure," *Psychophysiology,* vol. 24, pp. 375-425, 1987.

[122] K. Lange, "Can a regular context induce temporal orienting to a target sound?," *International Journal of Psychophysiology,* vol. 78, pp. 231-238, 2010.

[123] K. Lange, "The ups and downs of temporal orienting: a review of auditory temporal orienting studies and a model associating the heterogeneous findings on the auditory N1 with opposite effects of attention and prediction," *Front Hum Neurosci,* vol. 7, p. 263, 2013.

[124] A. Lampar and K. Lange, "Effects of temporal trial-by-trial cuing on early and late stages of auditory processing: evidence from event-related potentials," *Atten Percept Psychophys,* vol. 73, pp. 1916-33, Aug 2011.

[125] A. Jones, Y. F. Hsu, L. Granjon, and F. Waszak, "Temporal expectancies driven by self- and externally generated rhythms," *Neuroimage,* vol. 156, pp. 352-362, May 19 2017.

[126] V. Van Veen and C. S. Carter, "The anterior cingulate as a conflict monitor: fMRI and ERP studies," *Physiology & behavior,* vol. 77, pp. 477-482, 2002.

[127] S. Mantysalo, "N2 and P3 of the ERP to Go and Nogo stimuli: a stimulus-response association and dissociation," *Electroencephalogr Clin Neurophysiol Suppl,* vol. 40, pp. 227-34, 1987.

[128] A. Kok, "Effects of degradation of visual stimulation on components of the event-related potential (ERP) in go/nogo reaction tasks," *Biol Psychol,* vol. 23, pp. 21-38, Aug 1986.

[129] E. Jodo and Y. Kayama, "Relation of a negative ERP component to response inhibition in a Go/No-go task," *Electroencephalogr Clin Neurophysiol,* vol. 82, pp. 477-82, Jun 1992.