Charles University in Prague

Faculty of Science

Study programme: Biology

Kristýna Šafránková

Interval Timing and Emotional Modulation
Intervalové časování a emoční modulace

Bachelor's thesis

Supervisor: **PhDr. RNDr. Tereza Nekovářová, Ph.D.**
Consultee: **Mgr. Kristýna Malenínská**

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I declare that I wrote this bachelor thesis on my own and on the basis of consultation with my supervisor and consultee.

In Prague, 9.5.2018 ……..

Kristýna Šafránková

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Abstract

This bachelor thesis focuses on time perception, a field of study pursued extensively by psychologists, neuroscientists, and cognitive linguistic researchers. More specifically, this paper will examine the issue of "interval timing" (i.e. an individual's ability to perceive time intervals in seconds or minutes). Time perception is influenced by several factors, of which emotional modulation has been postulated as the most crucial. Examining the physiological mechanisms of emotional modulation and pacemaker-accumulator, the striatal model of time perception along with its role in emotional modulation form the contributions of this thesis.

Key words: interval timing, dopamine, emotions, the striatal beat-frequency model

Abstrakt

Bakalářská práce se zaměřuje na individuální percepci času, přesněji na tkzv. „intervalové časování" - tedy na to, jak jedinec dokáže odhadnout dobu určitého časového intervalu v rámci sekund až minut a jak je intervalové časování modulováno emocemi. Vnímání času je ovlivňováno mnoha různými faktory, ale emoce se jeví být jako jeden z nejzásadnějších, který může způsobit i značné zkreslení vnímání uplynulého času. V mé bakalářské práci se zaměřuji především na fyziologické mechanismy emoční modulace. Soustředím se hlavně na pacemakerový a striatální model časování a jeho vztah k emoční modulaci.

Klíčová slova: intervalové časování, dopamin, emoce, striatální model časování

Outline

1. Introduction

Existing in thought without a tangible form, time represents an example of an abstract concept. Both humans and animals are aware of time, which is an ever-present component of their lives. Although it is very difficult to evaluate long durations, both humans and animals possess the ability to estimate a time interval in seconds or minutes with precision. Time is a crucial element for all humans and animals and this is evident from our behaviour adjustment, highlighting an awareness of time. Moreover, our every action is shaped and guided by this kind of perception. However, there is an exception that allows us to modulate the flow of time. Time is omnipresent and it can be distinguished as either a physical or psychological time. The physical time is, when not considering the theory of relativity, constant and cannot be readily changed. However, in terms of psychological time, the brain serves as an exception to the rule that time cannot be changed and can therefore be shaped by our perceptions.

In order to acquire a deeper insight into this issue, it is important to examine which parts of the brain are involved in interval timing, what structures, and what type of neurons are responsible for our awareness of time. A vast amount of neurotransmitters is inseparably engaged in interval timing and the affective functions. The major time modulation factor, is intertwined in a close relationship and is carried out on the basis of neurotransmitters and other chemical molecules release. The aim of this work is to examine the role of the affective functions and their neuropharmacological background in relation to interval timing, its mechanisms, and modulation with the use of various interval timing models. References will also be made to recent findings in this field.

2.Interval timing

Interval timing is typically defined as the discrimination of time durations in the seconds-to-minutes range and possesses an advantage: increased flexibility in that it can run, stop/pause, and reset on command. Compared to circadian timing which is an unconscious process, this is possible because there is a potentiality of a cognitive control [1,2].

Humans and animals subjectively experience a very specific amount of time that ranges from seconds to minutes on a daily basis. This specific amount of time is referred to as interval timing and is essential for all human and animals in terms of their orientation in a space, decision-making, learning, and memory. This research aims to ascertain the underlying mechanism of the time perception and the neuroanatomical baseline, particular brain regions and circuits involved. The study of interval timing has led to the creation of timing models that serve as theoretical exhibitions of time processing

and its mechanism. An elaboration of this study will be provided in the following sections.

2.1 Properties of interval timing

Over the years, studies have observed and described the main properties of time in the second-to-minute range. One of the first, most important observed properties of the interval timing is the scalar property. The scalar property [3] is characterized as the inversely proportional relationship between time duration and the precision of time estimation (i.e. when the time duration prolongs the precision of time estimation decreases). Hence, the standard deviation of the timed interval grows proportionally to the mean of the interval and corresponds to the Weber´s law which can be applied on all senses as vision, smell, hearing, touch and taste. This law is based on human perception and the proportional relationship between the actual change in a physical stimulus and the perceived change (39).

3.Interval timing models

The understanding of time and its passage perception seems to be impossible on its own. Although humans and animals share a common sense of time, there have been calls for a deeper insight into the timing mechanism. The main problem arises when the subject of study is of a psychological nature, leading to the scientific explanations being quite ungraspable. The need for creating more comprehensible ways resulted in the establishment of timing models. In recent studies, various models have been proposed to offer a better explanation of the mechanism of interval timing and its processing - a task involving the estimation of time duration. Despite the still unresolved notion of an inner clock and the abstract nature of the entire mechanism, the models provide, at the fundamental level, an outline for estimation of time duration and it can serve as a guide for researchers pursuing more in-depth analyses of this issue. The most utilised models will be described and their limitations will be suggested in the following section.

3.1 The pacemaker–accumulator model

The pacemaker-accumulator model, as described in Arstila's paper [4], represents one of the well - known and most comprehensible models adopted in studies examining interval timing. One of the first schemes of this model was deduced from the primary experiments conducted in 1920 and created by Treisman [5]. Nevertheless, this model, which was very sophisticated at that time, is comparable to models subsequently developed in 1980 despite their different origins. The internal clock model described by Meck (1984) [6] is the current accepted model as the 'standard' model of internal time

representation.

The main prediction of any model is guided by the assumptions of experience. Whatever our brain perceives is first compared with information that is already present in our memory and is therefore familiar to us. Based on this mechanism, a certain event experienced at that moment would have to be compared with a duration stored in memory in order to obtain an accurate estimation of time duration of the event occurrence. The pacemaker-accumulator model operates on the basis of this assumption and its function can be summarized in the way of the pacemaker emitting pulses that correspond to a specific time interval. These pulses are further transferred via a switch to an accumulator and subsequently sent and saved in the working memory. The content of the working memory is compared with a reference time duration saved in the long-term memory. This comparison results in an appropriate response based on a decision rule.

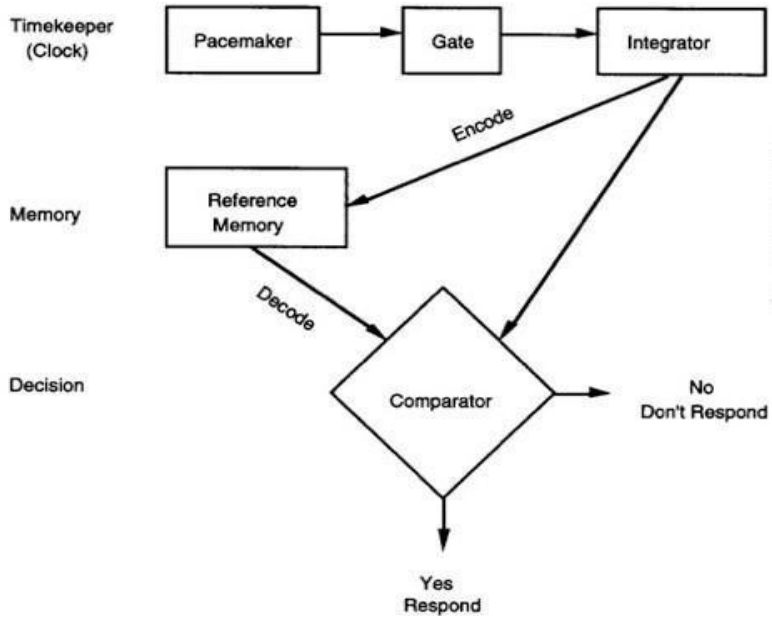

Fig.1 Pacemaker-accumulator model [7]

The mechanism of pacemaker-accumulator theory assumes that interval timing is composed of three abstract blocks: clock, accumulator (working or short-term memory), and comparator, all of which interact with each other. For any judgement of time to take place, some kind of stored information is necessary for the interval timing mechanism [8]. The main part of this inner clock mechanism is the "clock block" that is composed of pacemaker and the component generating pulses that we can link to beats of drums that produce a rhythm in music. Specifically, exuded beats are characterized by their interval lengths or analogically by their speeds. The pacemaker, as the base of the internal temporal mechanism, is highly dependent on a level of dopamine that has an effect on its pace which can either result in a faster speed or slower speed of the whole clock. Moreover, the pacemaker has

been discovered to be the main target for time-influencing drugs [6].

Another part of this mechanism that receives pacemaker generated pulses is called a switch. The main function of the switch is to transmit those pulses to another compartment - accumulator [9]. The interesting property of the switch is that it works in various modes. There are two different modes that are changing in the way of required action. The first mode is called as a run mode and the second mode is analogically a stop mode. The run mode operates with the pulses with the beginning of the signal and tracks the duration until the end of the action. The stop mode is in the game just when the stimulus itself is on. The switch can therefore be either open or closed. When the switch is in the closed mode, the pulses are allowed to go to the accumulator. Conversely, the pulses are locked during the open mode and they cannot be transferred and stored. Hence, the switch activity is being influenced by attention [10].

The sensory signal (e.g. the onset of a stimulus to be timed) initiates the counting of pulses from the internal pacemaker by an accumulator. The function of the accumulator involves storing all the pulses emitted from the pacemaker via the switch and saving them in the working memory (short time memory). The working memory holds and stores information of the action for a limited period of time that is defined by the duration of the trial [6]. Working memory is definitely inseparable from interval timing as it depends on the same brain structures of prefrontal cortex and basal ganglia, both of which play a major role in interval timing as well [7,11]. Reference memory stores information about the pulses as well but unlike the working memory, reference memory saves information about the event permanently. The reference memory serves as another important target of various drugs, hormones or chemicals that may modulate the interval timing. The last part of this psychological temporal model is called comparator. The comparator is unique as it is capable of making the final response while using a decision rule and the consequent response can be either positive or negative, depending on the comparison of the two values, one value from either accumulator or working memory with a value from reference memory [6].

3.2 Coincidence-detector model

This model type belongs to one of the recent interval timing models and was inspired by a neurobiological computational model. In comparison to other models, its understanding requires a deeper knowledge of physiology and the brain. Nevertheless, similar to other models, it is composed of three basic parts - clock, memory and decision.

An example of this model is the striatal beat frequency (SBF) model which provides an elaborate

insight into the mechanism of interval timing processing and perception of time. It also suggests what brain regions this mechanism might consist of. However, the experiments were based on research with animals and the main regions of a human cortex are therefore not specified. In the SBF model, the time processing is based on the activation of striatal spiny neurons that serve as detectors and this activation is produced via cortical neural oscillators when it occurs coincidentally [12].

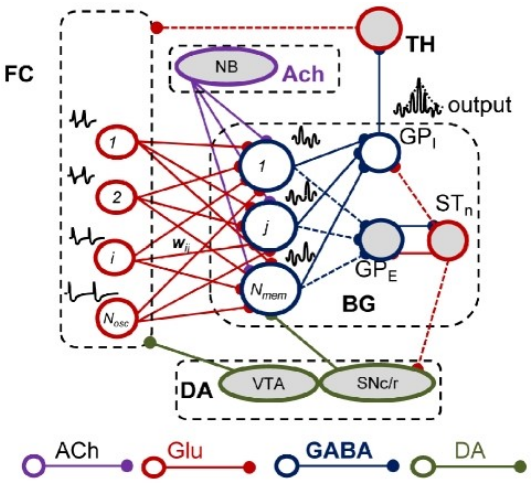

Fig.2 Striatal beat-frequency model. Schematic representation of the neurobiological structures involved in interval timing in the SBF model. Frontal oscillators are implemented as biophysically realistic neurons. ACh, acetylcholine; BG, basal ganglia; DA, dopamine; FC, frontal cortex; Glu, glutamate; GPE, globus pallidus external; GPI, globus pallidus internal; STn, subthalamic nucleus; SNc/r, substantia nigra pars compacta/reticulata; TH, thalamus; VTA, ventral tegmental area. Adopted from [12].

The activated regions in the SBF model are represented by striatum (both caudate and putamen), thalamus, and substantia nigra. Nevertheless, connecting the neuroimaging data of the brain regions when the subjects are exposed to a temporal task, and therefore supporting the SBF model function, is not doubtless. In the SBF model, particular brain structures are associated with specific timing functions. However, when imaging, other influences that may be involved in the activated brain structures such as general attention, memory or decision processes during the timing tasks have to be taken into consideration as well [13].

The function of cortical spiny neurons is fundamental for SBF model and is responsible for the production of coincidental beats that last for a certain period, giving rise to their categorisation as oscillators [1,14]. The activity of oscillators is affected by dopamine that is produced in two different ways - phasic and a tonic type of release [13]. In this model, the clock part starts its own timing with a reset of several oscillators that are firing with a different period. This resetting is triggered by the outset of a certain stimulus that causes a release of phasic release dopamine and the neurons start to pulsate at the same time. However, this state only lasts during the initial pulse and the periods of each oscillator quickly become out of phase with each other and different inputs have different oscillatory periods (5—15 Hz) [15]. Each of the cortical neurons oscillates with a constant phase whereby the frequency is attuned by the second type of release of dopamine, by the tonic release [13]. That represents a certain portion of the time duration when each oscillating neuron reaches its spike. At a particular point in time, it is possible to determine which oscillators are spiking at that moment. In

other words, the SBF model has proposed that the ongoing time duration is forming a particular cortical pattern with the assistance of multiple firing neurons that are oscillating with a different phase [15].

The onset of the stimulus starts the activity in the cortex that lasts across a variety of oscillatory periods. The striatal spiny neurons playing the crucial role in this model serves as coincidence detectors of a coincident activity of the subset of those cortical neurons. Striatal spiny neurons create almost 95% of the striatum [16] and the majority of the received inputs that are glutamatergic are from all parts of the cortex [17]. When the striatal neurons are 'reading' the cortical time code produced by oscillating cortical neurons, the occuring feedback and input of dopamine from the substantia nigra result in the strengthening of its connection in the synapse. The comparator/decision part occurs after the feedback when half of the phase of each oscillator is stored in a memory and the value in the reference memory is subsequently compared to the current accumulated value. The response is made upon passage of a similarity threshold. In the scenario where there is no feedback, the connection is weakened [15]. The detectors also signify the end of the timed trained duration. The information from the striatal spiny neurons is subsequently sent to a basal ganglia (globus pallidus, subthalamic nucleus, entopeduncular nucleus, substantia nigra pars reticulata), processed, and conveyed to thalamus for behavioral response. The flexibility of this model can be upgraded by the activity of the thalamus that can potentially and quite dynamically regulate the activity of cortex and striatum through the opening and closing of multiple loops [14].

3.3 The dual klepsydra model

To avoid focusing solely on one direction of the time processing models and their oscillations or pacemaker mechanism, another proposed model will be briefly described. The dual klepsydra model (DKM) of internal time representation and time reproduction, designed by Wackermann (2006) [18] is based on different principles as compared to previous discussed models. The process of time reproduction is based on comparing the states of inflow/outflow systems (leaky klepsydra) and if the states are considered as equal (reproduction), the timed duration is perceived as equal as well.

This model is characteristic for its two parameters, κ (outflow rate coefficient) and η (ratio of inflow rates). The notion of a flow (flow can be metaphorically linked to a water clock where the water change indicates the elapsed time interval) shares the same principle with the pacemaker-like models, where there is a stream of pulses being emitted. This is nevertheless the only common feature and DKM essentially differs in its concept of an integrator. The mechanism underlying this model could be liken to an image of two klepsydra. The klepsydra 1 is with the onset of a duration filled with the

inflow and after reaching a certain time (s) the inflow is stopped. The subsequent leaking is ongoing with a little decrement (κ). Klepsydra 2 starts to be filled with an inflow at the beginning of the reproduction phase until the states of both klepsydra are at equilibrium. When the reproduction state is reached, the presented and reproduction durations are subjectively perceived as equal.

As observed, a phenomena of short durations in the supra-second range occurs when the reproduced times were shorter and were specific for its progressive relative shortening [19]. DKM naturally explains this occurring distortion through the leaky klepsydra. The DKM is as a theoretical timing model very fitting to a notion of time processing and is able to explain occurrences that other models have to assume as an additional mechanism to the basic one. Nevertheless, the model lacks any physiological implementations and there is therefore space left for further enhancement.

3.4 Interval timing models and the emotional stimuli modulation

The changes in the perceived time resulting from emotional modulation induced by external stimuli are applied as the effect of neurotransmitters on timing models and their function. The key neurotransmitter is dopamine as it is released with increasing arousal which defines the valence of the experiencing emotion [20, 21]. The neurotransmitter dopamine is an essential molecule in interval timing and in adjusting the time perception regardless of the timing model. However, dopamine slightly differs in each model with its way of affecting the inner clock.

The most straightforward example of dopamine effects on the internal clock is evident from the pacemaker-accumulator model. The increased release of dopamine and its excessive synaptic presence is responsible for the acceleration of the pacemaker and its rate of emitting pulses. The more pulses are emitted, the higher number of pulses is accumulated and time is experienced as dragging. Conversely, a lower level of dopamine below the effective level of dopamine in the synapse is assumed to decelerate the pacemaker and time is perceived as passing faster [6].

In the discussed SBF model, the effect of dopamine release is considered to have an ability for modulation of the speed of the internal clock by modifying the oscillation frequencies of cortical neurons [22, 23]. As briefly mentioned in the mechanism of SBF model, dopamine is released in two different ways, phasic and a tonic type of release [24]. Although the dopamine molecule is the same, the type of its release defines how the mechanism is modulated. The phasic release could be linked to a ´start gun´. It serves as a signal to synchronize the cortical oscillations by indicating of the outset of the stimulus and the impact on the spiny neurons is present in their resetting of the membrane and preparing for the detection of the oscillations. The role of the other type of release, the tonic release,

involves directly attuning the frequency of oscillation of the cortical neurons. Thus, the frequency the neurons are oscillating with defines the speed of the internal clock. The dopamine tonic release increases during a high-arousal state and causes an acceleration in the speed of the clock, resulting in the overestimation of time. Thus, the perceived duration is judged as being longer. The decreased release of tonic dopamine is characterized by the deceleration of the clock and therefore, time is underestimated [13]. This principle of clock speed resembles the pacemaker-like mechanism.

The emotional modulation of perceived time is explained with the application of DKM. It is suggested that the distortions in time perception are caused by changes in integrator flows and inflows are assumed to be coincidentally fluctuating. As the stimuli of high biological relevance culminates in arousal, a hypothesis that the observed effects of arousal (increased level of dopamine and speeding up of the internal clock) are caused by a temporary increase in the neural flows is proposed. Thus, the difference between arousing and emotionally neutral conditions lies in a high probability detectable by the inflow ratios [25].

3.5 Pros and cons of interval timing models

However, models suffer from inaccuracies or are unable to explain all the occurring influences and modulations of time. In reality, there are many qualities of timing models that correspond to the real-life experience of time processing and its perception.

To evaluate the pacemaker-accumulator model, there are some notable advantages apart from some neurobiological implausibilites due to the abstract nature of this model. This model is generally very straightforward, inviting its application to many tasks and experiments that include various kinds of species [1]. Considering its simple design, the predictions of the time modulation using this model are surprisingly mostly accurate (higher-arousal stimuli) [6]. Its division into clear, individual parts: clock, memory, and decision, makes it possible to associate these components with particular brain structures [23] and integrate them into neurotransmitter systems [7]. However, neural mechanisms that implement it have yet to be discovered.

The PA model has been criticized for its inadequacies of the switch grounds. The attention is supposed to have an effect on the switch operation but its direction to the external stimuli means that the influence on the switch is indirect because the switch operates between pacemaker and accumulator and it has no access to the external stimuli. There is, thus, a shortcoming in a clarification of the

internal response mechanism of the switch and all the elements the duration estimation requires [4].

With regards to SBF model, one of the advantages of this model in comparison with the PA model is its consistency with the known neuroanatomy and neuropharmacology of interval timing. Moreover, it is possible to formulate testable predictions concerning the functions of its components despite the fact that the SBF model was based on research with animals and does not specify the specific regions of the human cortex. [26, 13, 27].

The biggest support for both SBF and PA is that both models are based on the dopaminergic activity of frontostriatal loops, for example, that are underlying the duration processing. A dysfunction of these loops has an effect on a dopamine release that is manifesting in a way of underestimating perceived time. The decrease in a dopamine release results in the slowing down of the clock system and therefore this evidence highlights the accuracy of both timing models [15, 14].

4. Neuroanatomy of interval timing

The results obtained from several experiments conducted over past decades provide us with a certain amount of information concerning parts of the brain involved in interval timing and direct information about what nuclei are associated as well [15].

4.1 Basal ganglia

Basal ganglia are among the most important subcortical structures that play an essential role in timing [45]. Research in this area suggests a concept of a hypothetical ‘‘internal clock´´ situated within the basal ganglia. The support for their involvement comes from the nigrostriatal dopaminergic system together with a recent identification of cannabinoid receptors in the basal ganglia and their interaction with dopamine systems. There was a hypothesis that in contrast to the cerebellum, the basal ganglia are considered to be responsible for time durations from the seconds to minutes range [7, 46]. However, the results from a different study contradicted this hypothesis and basal ganglia were activated in the timing of both short (milliseconds) and long (seconds range) intervals [27].

The basal ganglia form an inseparable part of a whole timing brain circuit and its contribution lies in the transferring of the excitatory input received from the cerebral cortex (and from thalamus) to the striatum. Striatal neurons are the essence of one of the timing models (SBF model) and are generally

without particular activity until their activity is generated by this excitatory input [47].

4.1.1 Striatum

Striatum belongs to the most significant structure of basal ganglia that is essential for interval timing and, as was mentioned earlier, is also in a tight connection with a working memory. The dorsal striatum has been suggested to possibly serve as a 'core timer' because its activity is observed in both duration reproduction and duration perception tasks in the subsecond and supra-second ranges [23,48,49].

The support for these areas of the brain to be involved in a time processing was provided by Coull et al. (2004) [11] who conducted an experiment focusing on attention. They asked participants to alternately direct their attention to either colour stimulus or time stimulus. They used a method of fMRI (functional magnetic resonance imaging) for identification of the brain regions employed in attentional modulation of time estimation. Working with an assumption that when the attention was drawn to colour, and when the areas fundamental for colour perception were activated, the same principle will work with time perception. Thus, this method helped to identify the neuroanatomical essence for time processing. The results showed that when the attention was directed to time, the activity increased in premotor and supplementary motor areas, frontal operculum and dorsolateral prefrontal cortex, temporal and parietal cortices, as well as the putamen. Such activity implicates a formation of the cortico-striatal networks and a tight cooperation of this brain regions.

In a recent study, performed namely by Matell et al. (2003) [23], they were concerned with cortical and striatal neurons and what role they play in interval timing. The findings from their experiment suggest that within the dorsolateral anterior striatum and anterior cingulate cortex, there is a subgroup of neurons and this single group of neurons can encode a specific amount of time. It was observed that near the time when a reward was expected, the temporal neurons gradually increased their firing and if no reward was given after reaching this period, the firing declined. The same pattern was observed with cortical neurons but the effect was more subtle than with striatal neurons. These data suggest an important role in the context of time perception.

On the basis of cortico-striatal networks, and most importantly on the activity of striatal spiny neurons, one of the timing models - Striatal beat-frequency model was formed. Nevertheless, there have been more brain regions being proposed as necessary for the timing. The following of the signal

pathway from the cortex, which transfer input to the striatum, and the thalamus, a brain relay nucleus that receives input from the basal ganglia and sends output back to the cortex [13], are also anatomical areas that influence timing behavior and therefore the cortico-striatal circuit is being extended to an anatomical pathway, the cortico-striatal-thalamic-cortical loop [14]. This culminates in an ascertainment that even spatially distinct brain structures share similar hemodynamic changes simultaneously and therefore provides evidence for an interconnection forming not just of functional circuits but also forming of a whole functional network that promises way more space in research of timing processing [13].

4.1.2 Substantia nigra

It is a structure of basal ganglia located in the midbrain that is strongly involved in timing. The SN incorporates dopamine-releasing neurons and its dysfunction or loss of neurons results in insufficient dopamine levels and Parkinson's disease. This small structure is known to be greatly enriched with dopamine receptors, its crucial importance in time perception will be described later. The former notion of the nigrostriatal dopamine system exclusively involved in motor function, however, has changed over time and it is now generally accepted to be involved in the attentional set switching, error prediction regarding the occurrence of rewards, timing and time perception [2]. The evidence for its integration was provided by lesions in the substantia nigra pars compacta that result in an elimination of timing [7,22]. The neurons within substantia nigra were suggested to form one of the basic components of the timing model, namely the pacemaker-accumulator model. The pacemaker of this model is supposed to be created by the rate of the neuronal firing that is modulated by the effective level of dopamine and the integration of the emitted pacemaker pulses is mediated via the striatal neurons [7,15].

4.2 Frontal cortex

The frontal cortex has been discussed previously for its cooperation with basal ganglia and as a part of cortico-striatal circuits. Additionally, diverse lines of evidence emphasized the function of the frontal cortex, specifically dorsolateral prefrontal cortex, and its high involvement in the ability of time perception [11,50,51]. Its role in time perception is also suggested by the involvement of prefrontal cortex in attention and working memory that is essential for timing as well [32,52]. The prefrontal cortex is believed to be important for time estimation of intervals in the seconds-range. This assumption corresponds to results of the transcranial magnetic stimulation (TMS) of a prefrontal cortex that impairs timing in supra-second durations [53]. This specific frontal cortex stimulation also confirms neuropsychological observations of patients with this kind of lesions that implies deficits in

the timing of longer durations [54,55].

4.3 Cerebellum

The cerebellum is also classified as one of the most important subcortical structures that play an essential role in the timing [45,56].

Nonetheless, there is ambiguity surrounding the cerebellum timing range. The cerebellum was formerly thought to just be involved in a connection to a millisecond timing and there have been reported deficiencies in duration discrimination with 400ms intervals in patients with lesions in the cerebellum [57]. However, more recent evidence suggests an impairment in discrimination of the both short (400ms) and long intervals (4s) [58]. The cerebral lesion too suggests an impaired production of an interval as long as 10s [59].

The cerebellum is, thus, observed as being active in both millisecond and interval timing (second-to-minute range) tasks. However, there is no clear border demarcating the difference between these two kinds of timing: when a certain brain structure is still active and when a different neural region takes its turn in time processing. Nevertheless, several attempts have been made to distinguish distinct separate neural correlates participating in sub-second and supra-second timing [60] but the meta-analysis of neuroimaging studies of perceptual and motor timing failed to differentiate distinct cerebellar roles for long and shorter interval [61].

These brain structures described are not, however, the only ones involved in interval timing. Another structure that is active in the context of timing and is involved in working memory, an important component in the AP model, is fimbria fornix. The lesion of fimbria fornix causes the inability of transferring the information between the accumulator and the working memory or between working memory and comparator. The reason for this inability is that the connection to the hippocampus is removed and it results in a permanent distortion in the remembered time of reinforcement. Thus, as shown in some of the experiments conducted on rats, a lesion of fimbria fornix creates a leftward shift [6].

As we can see, the contribution of the lesion studies is prominent and the lesions or impairments to the brain offer the most informative value of how the time is being processed.

5. Methodology of the experiments

No experiment is universally applicable for acquiring of significant data and there is, therefore, a need for utilising various means of evidence-gathering for understanding the mechanism of the inner clock. The information was systematically collected from many experiments conducted over past decades and on the basis of evidence gathered, for example, from time distortions and defects in the time perception. Diverse lines of evidence suggest for instance a tight relationship between defects in interval timing and some neurodegenerative disease such as Parkinson's disease or schizophrenia. Other experiments were performed with help of human volunteers or through the adoption of pharmacologic manipulations. This is just a small drop of water in the sea of possibilities and the following section will focus on the main scientific methods used.

5.1 Time discrimination tasks

There are some specific ways of examining the ability of interval timing and the perception of time in general. Various psychophysical procedures focusing on temporal discrimination have been conducted in order to obtain an overall understanding of the concept of timing. The examples of the tested subjects listed are for better illustration of the methods. However, all of the described time discrimination methods can be used on both animals and humans. Nevertheless, the procedures can revolve around different sensual stimuli that are being presented. Such stimuli can be acoustical or either visual or even their combination but the outcomes may differ [28].

The next division of the time judgment is distinguished according to awareness of the temporal stimuli. This is known as prospective and retrospective timing. The prospective timing is when the subject is informed that the timing is involved and the timing depends on attention. Retrospective estimation is when the information about timing is not provided until the end of the trial. The time judgment, therefore, depends on memory for temporal information [29]. However this type of method (retrospective) is only possible with human subjects. The results differ in the accuracy of the time estimation. People possessing prospective timing tended to be more accurate in judging time but fared worse in non-temporal task performances. The retrospective timing was conversely less precise in time estimation but more successful with the non-temporal task [30].

The principles of the time discrimination procedures are also used for studying the consequences of neurodegenerative and neurological disorders (such as Parkinson’s disease, Huntington disease etc.), lesions of brain structures (basal ganglia, frontal cortex, thalamus) on timing. The differentials in time perception are compared between ongoing experiments whereby the patients are on or off medication [3]. The three main procedures used in a temporal examination will be presented in the following

sections and all of them are used for their contribution to an interpretation of the change in the speed of the internal clock, which could be an increase (leftward shift) or a decrease (rightward shift) [31].

5.1.1 Bisection procedure

The primary aim is to teach animals how to respond differently to particular temporal stimuli. Experimental animals are trained to press a lever according to the length of the interval duration. When a short stimulus duration is presented (e.g. 2 seconds) the right lever ought to be pressed and the left lever after the occurrence of a long (e.g. 8 seconds) stimulus duration. This procedure was used for example by Maricq (1983) [32] or Church and Deluty (1977) [33]. Once the animals have been trained to respond differently to a stimulus, the interval durations that are distinct from the original presented durations that have been trained are incorporated into representation and intermixed with the short and long durations.

5.1.2 Fixed-interval procedure

This procedure is based on a cycle that consists of a stimulus indicating the start of the duration and an example of this stimulus can be seen in a form of a light that is turned on. When the stimulus is triggered off, after an amount of time has elapsed (e.g. 30 s), the response has to be made in order to receive reinforcement or feedback before the stimulus is terminated [15]. This procedure involves examining the ability of the exact estimation of a certain duration. In practice, rats are test subjects used to estimate their time duration after a light signal with the highest precision. When the rat enters a food cup after a target duration, the food is delivered and the stimulus is terminated [31]. After a period of no stimulus, the light can be turned on once again and the cycle is repeated. The outcomes of this temporal bisection procedure serve as evidence supporting the four main principles of timing that were pointed out by Gibbon [3]. The first principle, known as a timescale invariance, shows the overlapping of the estimations of different interval durations when plotted on a relative scale. The other principles of proportionality, the scalar property and Weber´s law of timing have been already discussed in the earlier sections highlighting the properties of the interval timing.

5.1.3 Peak-interval procedure

The third psychophysical procedure is similar to the previous fixed-interval procedure although it differs slightly in the way that the subjects are confronted with two cycles instead of one. The first cycle is identical with that from the fixed-interval procedure and it is therefore called a standard cycle. The duration that should be timed is being reinforced. In the second cycle, also known as the peak cycle, the response after the stimulus in the form of light is not followed by any feedback or the termination of the stimulus. This second cycle is also used as a probe cycle. Thus, the animal is

exposed to a significantly longer stimulus duration in the peak-cycle than it is the target duration and the response has no effect for a reward. The presentation of the two cycles is randomly generated by a computer [31]. Church (1978) conducted some experiments with the peak-interval procedures and in these trials, the rates of forming responses that were trained for the stimulus increased with the outset of the stimulus and reaches the peak just around the time when the response had been reinforced, the duration that should be timed by the animals. The rate of response-making displays a decreasing trend after reaching the peak time [34]. The outcome of this trial is a Gaussian-shaped response function that has its peak very close to the criterion time [15].

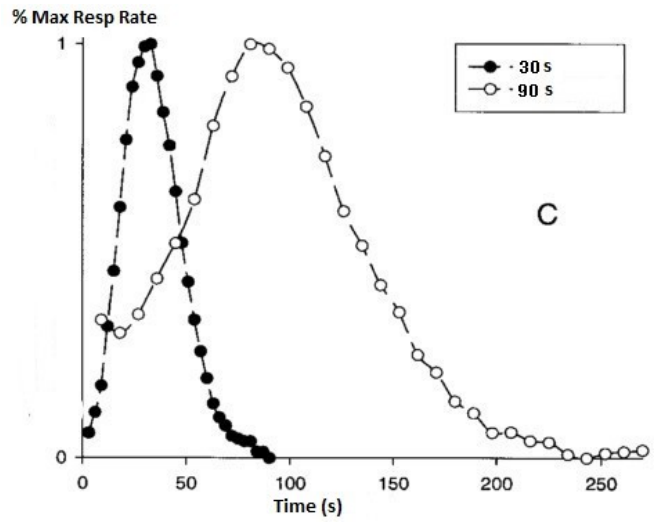

Fig.3 - Temporal estimation data using peak-interval timing procedures [14]

5.2 Pharmacological influence

The internal clock and memory are indirectly ran and adjusted by chemicals, hormones and other molecules produced by body itself that are releasing according to current body or mental states. A key question that emerged involved understanding whether it would be possible to specifically adjust the internal clock activity by pharmacological manipulations through the artificial application of drugs or inducing a higher release of neurotransmitters or hormones before observing changes in the responses for temporal trials.

In general, drugs have been used due to their potency of direct or indirect impacts on neurotransmitter release and a co-action with corresponding receptors. The experiments suggest that neuroleptics are used to influence the effective levels of this neurotransmitters, thus drugs serve as an intermediator. There are few kinds of pharmacs that were ascertained to have specific time modulating effects and as an example, the administration of neuroleptic drugs in sake to influence the time perception

resulted in a decrease and increase in subjective time estimation [32].

5.2.1 Dopamine

When considering the drug administration, the catecholamines such as dopamine or noradrenaline are crucial in speeding up the inner clock as they have a potency to directly influence and target a single component of the clock mechanism.

Dopamine is known for its multiple binding sites and it forms a total of five different kinds of receptors: D1, D2, D3, D4 and D5 [107]. Each of the dopamine receptors has some particular function but the main aim was to detect which receptor is essential for interval timing and its modulation.
There are 3 different dopamine receptor subtypes that the neuroleptics cooperate with but on the other hand, as was reported by Meck (1995), they also interact with another neural receptors such as alpha noradrenergic and serotonergic sites which makes it harder to validate what the real factors of time perception modulation by pharmaceuticals are. However, the strongest correlation corresponded to dopamine D2 receptor for all of five different neuroleptic drugs applied in Meck´s experiment [35] which were compared with an affinity for each type of the dopamine receptors. The affinity of dopaminergic antagonist drugs for D2 receptor has been correlated with the degree to which the clock component is slowed down and this receptor was marked as essential for interval timing.

5.2.1.1 Dopamine influencing drugs

There are two types of neuroleptic drugs that provide distinct effects on the release of dopamine and, therefore, interval timing [36]. The first group (e.g. methamphetamine, cocaine) has a dopaminergic agonist property [7,10]. These pharmaceutics share a relationship with the essential neurotransmitter dopamine by influencing its effective levels and they are primarily binding to D2 receptor. The dopaminergic agonist property is responsible for an increased dopamine release and its actuation also restricts the dopamine re-uptake to a cell. In virtue of the excess dopamine in a synapse, the effect on an inner clock results in an leftward shift [6].

The second group of neuroleptic drugs has an opposite impact on inner clock speed and therefore they work as dopaminergic antagonist [12,37]. This antagonistic property operates with and blocks the dopamine receptors [6]. While the dopamine receptors are blocked and cannot respond, the effective level of dopamine is considerably decreased and as a result the time is overestimated in time interval estimation tasks [37]. In other words, low levels of dopamine in the synapse have an impact

on the inner clock in terms of causing a rightward shift.

5.2.2 Acetylcholine

Acetylcholine is another neurotransmitter that is inseparable from time processing. Its release and effective level modulate time perception and can result in a leftward or rightward shift depending on the level of the neurotransmitter in the synapse. In terms of a pacemaker-accumulator model where dopamine corresponds to a pacemaker rate, the acetylcholine is related to reference memory. The increase in the effective level of acetylcholine may be induced by an administration of for example physostigmine [36]. This manipulation works by inhibiting acetylcholine degrading enzyme. Thus, there are more neurotransmitters present in the synapse and the increased effective level of acetylcholine results in a faster memory storage and enhanced information processing. In other words, there is an increased speed at which information is transferred from the accumulator into reference memory and the remembered duration of events is shorter. Conversely, the decrease in an effective level of acetylcholine (e.g. a lesion to the medial frontal cortex, atropine administration) results in a decreased memory storage speed and produces a gradual rightward shift in the timing [7,36].

5.2.3 Glutamate

Glutamate, in tandem with dopamine, forms an integral part of the internal clock mechanism. It has a specific role in the cortico-striatal circuits. Therefore, it enables the activity of the striatal beat-frequency model. The glutamate is active in pathways connecting cortical and basal ganglia structures that are involved in working memory and interval timing [13,15]. The excitatory glutamatergic pathway creates several parallel loops via connecting the dorsolateral prefrontal cortex with thalamus and posterior parietal cortex [38]. The glutamate has also the potency to regulate the activity of dopamine as its glutamatergic pathways interact with dopamine. Moreover, specific glutamate receptors are sensitive to dopamine and their dysfunction in the prefrontal cortex and hippocampus lead to an increase in the dopamine release in the striatum [39].

5.2.4 Tetrahydrocannabinol (THC)

Apart neuroleptics, the effects on interval timing were tested by the administration of the psychoactive drugs for their effects on time perception. In the experiments, humans [40] and animals (e.g. pigeons) [41] were tested under the influence of marijuana as marijuana is known for its cognition-altering ability and the most perceptible effects inhere in the distortions in their time perception. The effect on time perception is most probably caused by their binding to cannabinoid receptors in the basal

ganglia that interact with dopamine systems [7]. When people are under the influence of THC (tetrahydrocannabinol), they usually report that events and thoughts seem to occur more smoothly and time passes very slowly [42]. The administration of THC was realized with marijuana cigarettes with a low (placebo) and high potency and the participants were trained on an interval bisection procedure by judging 2 durations as ´short´ (2s) and ´long´ (4s). The results confirmed the previous findings and the THC compared to placebo resulted in a leftward shift in time estimation which means the time was under the drug influence overestimated [40]. The THC is found to be increasing the activity of dopaminergic neurons [43] and the overestimation of duration might be the result of an increased level of dopamine in the synapse that was reported to increase the rate in which the pacemaker is emitting its pulses. This study is, therefore, consistent with Meck´s proposed neuropharmacological model of timing [7].

On the other hand, the THC has an effect on the release of acetylcholine that determines temporal memory. However, THC is anticholinergic, so the neurotransmitter release is restricted and the effective level of the presence is decreased [44]. The scantier occurrence in the synapse causes a decrease in a memory-store speed and produces a gradual rightward shift. Thus, the effects of THC result in an alteration of clock speed and memory-storage speed that, however, work contrarily and their effects may manifest at different phases [7]. Apparently, further experiments that would unmask the intertwined effects of clock speed and memory-storage are needed.

A noteworthy observation is that the interval clock shift can be possibly achieved by the application of a modified diet [6] beside an administration of some dopamine-influencing drugs. For instance, introducing food high in carbohydrates (sucrose) resulted in a decreased pacemaker speed whereas food high in protein (casein) in the rats' diet was responsible for an increased pacemaker speed. As we can see, the time modulation might be caused by various ways that we may not be aware of and these might contribute to false interpretations of some results.

6. Neuropathology and time perception

One of the most significant contributions to interval timing research comes from neuropathological diseases, along with their effects in terms of impairments to time perception and modulation of duration estimation. The most studied diseases are Parkinson's disease and schizophrenia as they depend on the brain structures and dopamine level which the interval timing relies on as well.

6.1 Parkinson's disease

Although the most obvious symptoms of Parkinson's disease are one of motoric nature (inability of movement coordination), this disease is also associated with non-motor symptoms. One of the experiments focused on temporal estimation as a non-motoric symptoms [62]. Authors used a method of temporal discrimination thresholds (TDT) where a wide range of time intervals was given that were paired with a sensory stimulus (auditory, visual and tactile) in order to differentiate between two subsequent stimuli as separate in time. Parkinsonian patients were compared with a control and the results showed that they generally require longer time intervals to be able to discriminate between two paired stimuli. The results from their experiment using TDT, therefore, indicate a slowdown in their ´internal clock´ what may be also consistent with the decreased level of dopamine in the brain caused by a loss of substantia nigra´s dopaminergic neurons [63]. As a loss of dopamine causes abnormal functions of basal ganglia and results in a motor symptoms of Parkinson's disease, it may have also effects on the speed of pacemaker of the internal clock.

6.2 Schizophrenia

Another neuropathological disease that has been studied in relation with interval timing is schizophrenia. As it was discussed in the previous section, the cortico-striatal circuits are significantly responsible for encoding and processing of temporal information [13]. Interestingly, schizophrenia is associated with deficits of neural communication within cortico-cerebellar and cortico-striatal brain circuits as well [64,65]. There is an analogy between the neural circuits underlying the internal clock mechanism and the circuits´ inactivity resulting in schizophrenia. Thus, we have a source of information providing better understanding of temporal deficits associated with this disorder.

Patients diagnosed with schizophrenia were tested on their estimation of short time intervals and their time experience consistently resulted in an estimation of the given duration to last longer than it actually lasted. Therefore, these results may indicate a possible faster run of their ´internal clock´ [66,67]. Time is felt to pass slower with patients suffering from schizophrenia because of more pulses

accumulated in a unitary interval of time than for control participants.

In relation to schizophrenia, a dopamine hypothesis that postulates a hyperactivity of dopaminergic transmission at the D2 receptor has been proposed. However, some of the prior experiments, did not offer any information about the dopamine levels in a synapse at a baseline state of schizophrenia patients when there was no influence of nonphysiological administration of, for example, amphetamine [68]. Different experiments tested the synaptic dopamine level without any pharmacological interference and their results suggested that in the brain of schizophrenia patients, a significant majority of sites of striatal D2 receptors are occupied with dopamine even during the baseline state.

When considering the effects of dopamine in the brain on the speed of the ´internal clock´, the increased dopamine in the synapse is responsible for the pacemaker's emitting of more pulses. Thus, we are standing in front of this quite straightforward analogy between schizophrenia patients who constantly overestimate the time duration and the increased dopamine level in the synapse of those patients might be the factor of this time modulation.

7. The effects of arousal and attention

7.1 Attention

The noteworthy influence that is being seen to be responsible for a considerable impact on the inner clock and time perception is attention. The role of attention has been already mentioned in a context of the switch activity, part of the PA model. The attention is proposed to be directed consistently to the switch in order to keep the connection between pacemaker and accumulator closed. Otherwise, the switch would tend to open simultaneously and the number of accumulated pulses would get reduced. This state is also called a flickering switch [10].

Depending on the direction the attention is paid to, the time judgment results in either overestimation of time when attention is directed to internal clock whilst (waiting for a bus), or underestimation of time when attention is paid to some distracting non-temporal stimulus. The effect of attention can be generally explained with a use of the internal clock. When a person is exhibited to a temporal task and at the same time there is another distraction task which is non-temporal, the attention is redirected and as a consequence, the pacemaker activity is restricted and lower number of pulses is accumulated. This redirection of attention, therefore, produces a subjective impression of a shorter time has passed.

This example is also known as an attentional gate model (AGM) [69].

7.1.1 Attentional gate model

The pacemaker is emitting pulses and the rate during high-arousal stimuli is affected. The innovation of the attentional gate model proposed by Zakay (1994) [103] inheres an added component of the clock model in a form of an attentional gate which stands between the pacemaker and switch. When the pulses reach the attentional gate, further action is conditional on the amount of attention which is allocated to timing. More attention is paid to timing the moment the switch is open and more pulses are allowed by the gate to pass to a switch. The subsequent steps involved are identical with the original model and the number of pulses counted by an accumulator and then compared with the number stored in reference memory is given by the duration elapsing between the 'open' and 'close' mode of the switch. Thus, according to the AGM, the attention allocated to a threat caused an increase of arousal and it should occur as more attention is paid to time and therefore overestimation of the duration.

7.2 Arousal

A major factor that has been reported to change the perception of time very effectively is arousal. An arousal may be induced via various ways. The first way that was already discussed in the previous sections is through altering dopamine levels by administration of drugs. Another option is through metabolic processes when a body temperature is altered. The resulting clock shifts were induced by a fluctuation of the dopamine level since excessive dopamine presence in the synapse imply a higher arousal [20,21].

When discussing the influence of attention and arousal on time perception with use of timing models, we face contradictory findings. The higher arousal was reported to result in speeding up the clock but concurrently, arousal diverts the attention from inner clock to external stimuli that caused an arousing state. The attention is conversely assumed to result in underestimation of time duration when attention is not paid to an internal clock system. On the other hand, attention contributes to the effects of high-arousal emotion on time perception [70]. The resulting problem is that a threatening stimulus results in an increased arousal as well as drawing attention. This dilemma can be partly resolved by an evidence of the short-lasting effect of arousal on timing and in contrast, the attention effect can persist for much longer durations [71]. Overall, we can assume that arousal and attention are independent but interrelated. Knowledge of relation between attention and arousal cannot be, however, sufficiently explained and predicted by the framework of the SBF model or even by the pacemaker-accumulator

model [15,72].

As a consequence of various insufficiencies of internal clock models, a new theoretical approach [73] has been proposed to contribute to better understanding of the processes underlying the time perception distorted by affective functions. This newly designed approach assists in demonstrating the relationship between attention and arousal that underlie such time distortions.

The essential part of this new theoretical model proposed by Lake et al. (2016) [73] is the estimation of a certain time triggered by an emotional event. The effect of the emotions involves the orientation of the attention to these arousing state away from an internal clock. In addition, the level of the emotional valence is supposed to modulate the power of the initial influence on time perception. Apart from the role of attention, an increase in overestimation for the duration in a second-range is believed to be caused by a short-term physiological arousal arising upon the emotional stimulus onset. The intensity of the arousal, depending on the initial emotion valence, defines the effects on time perception and when the level of arousal returns to baseline.

In the period of emotional influence when time is most susceptible to changes, there are processes involved in the sharing of the attention and working memory between timing and emotional process engaged in addition to the physiological arousal effects. Upon the onset of the emotional stimulus, the arousal initiates the time modulation and the influence of attention becomes gradually involved too as time elapses, contributing to the relationship between attention, arousal and the inner clock. To conclude this proposed model, attention is being engaged to the time processing with a consideration of the emotional stimulus relevance. The more emotionally relevant a stimulus is, the more attention is given to the duration timing and it results in the overestimation of the subjective time duration [73].

The classical models tend to couple an effect of attention or arousal with particular components of the models that consequently results in a particular time modulation and this new theoretical model attempts to evade this too straightforward explanation.

8. Emotions and interval timing

Although emotions are sometimes considered as psychological/social constructions, they are inseparably related to physiology and brain functions. Whatever happens in our body, and it does not matter if it is either in our muscles or our head, has a physiological substrate. Emotions are induced with an emotive stimulus that triggers the generation of complex affective states [74] and our perception of time is undoubtedly colored by experiencing such affective states. After decades of

discussion, there is now a strong agreement about the evidence of universal emotions that are shared among people regardless of age, sex, race, location, and education [75]. The current convention is composed of five basic emotions, namely anger, fear, disgust, sadness, and happiness. All these emotions have been claimed to be universally expressed and recognized in people around the world and they are supposed to be hard-wired into brain circuits by evolution [75,76,77].

Out of various kinds of stimuli, people are only aware of the effects of attention and emotion on the passage of time. Thus, there is a strong evidence for emotion integration in time perception. From a set of emotions, sadness and happiness are judged to affect the sense of time's passage most perceptibly [78]. Thus, the survey results correspond to common expressions such as "time flies when you're having fun". Conversely the feeling of sadness induced as well by seeing a sad person, or listening to sad music has a similar manifestation as in the case of depression and the difference between physical time and self-experienced time is reported as dragging [79].

8.1 Sadness

When people are experiencing sadness, they often report that hour seems to last like a year [104]. Nevertheless, when examining the time perception with people with depression that is tightly connected with an emotion of sadness, their time estimation results differ from their experience. One of the experiments was based on bisection task procedure - short (400 ms) and the long (1600 ms) standard signal durations and the data were compared between depressive participants and non-depressive participants. The results were surprisingly distinct from the reported experience as depressive participants judged time to be relatively shorter. Furthermore the more the depression scores increased, the shorter the signal duration was judged to be. The effect on the speed of internal clock that is running more slowly can be explained as the effect of lower level of arousal and that fewer pulses are accumulated per unit of time, thus, the duration is judged to be shorter [105]. Taken together with results from different experiments [108,109], it is hard to drawn a conclusion what effect the sadness has on time perception and further research will have to investigate whether there is any other related time distorting cognitive mechanism.

8.2 Happiness

Even though happiness is judged very subjectively and for everyone is induced by some different stimulus, the reported perception of time when feeling happy is consistent, thus, time flies. The happiness is a positively arousing emotion and with an usage of both SBF and PA models, we can assume that the induced higher level of dopamine results in an acceleration of inner clock. However, there is a correlation between happiness and attention that is more relevant prior to arousal. It was ascertained that more the subject is happier the more is inattentive [106]. That could be explained as the attention is not allocated to a timer and fewer pulses are accumulated per unit of time that results in time to be evaluated as shorter than the real past time.

8.3 Life - threatening events effect on time perception

Recently, there has been a growing body of experiments examining emotional influence on perceived time. The experiments utilised various kinds of methods in order to arouse emotions and subsequently test the changes of time perception. Although the attempts are not equally successful, among the most interesting studies are the ones comprising life-threatening events.

When an individual is exposed to an event that could be potentially life-endangering, the level of arousal is, with a high probability, greater compared to events when the individual experiences happiness. The emotional arousal also plays an important role in the way a memory is being stored [85]. The higher the arousal is induced by an emotion, the more vivid the memory is with an increased retention [86] which may play a role in a subsequent retrospective judgment of time.

8.3.1 Fear

Besides, the focus of some studies was orientated predominantly on the other basic emotions such as fear or anger. These emotions are induced with a high-arousal stimulus and therefore the time distortion is even more noticeable. When there is an experience of negative, high-arousal emotional stimuli (seeing a dangerous animal, angry person) the defense reaction for survival are triggered which corresponds to acceleration of the internal clock rate [80,81]. The higher arousal caused by a present of some threat results in the body activation of a stress response, a state of alarm, that brings about changes in the autonomic (increase in respiratory, heart rate) and somatic (facial and bodily motor expression) nervous systems to prepare the organism to act as fast as possible (fight or flight) [78]. When the subjects were exhibited to for example faces expressing anger [82], pictures with a very unpleasant content such as mutilated bodies or pictures evoking danger (e.g. a snake) [83,84], all the experiments offered similar outcomes. Thus, negative, high-arousal stimuli result in judging the time spent watching the pictures to last longer than neutral stimuli. Though, the sensitivity to time

was not anyhow changed.

The key emotion that is being experienced in life-threatening situations is fear. The subtending brain structure of this emotion is amygdala which is highly enriched in D1 and D2 receptors [87]. The dopamine release is observed when experiencing stress within amygdala [88] and the role of this release resulting in fear/anxiety is to relieve the amygdala from its cortical brake and enable the individual to cope with threats via binding of the released dopamine to a D1- and D2-receptor sites [89,90]. Thus, fear is highly dependent on the dopaminergic system of amygdala [91]. This negative emotion is induced when facing a threat and is considered as a high-arousal stimulus, therefore triggering a process that results in judging of the experienced duration to last longer.

We can logically assume that high-arousal stimulus speeds up the internal clock system involved in time perception. The distortion of perceived time that is induced when a human or an animal is experiencing fear corresponds to the pacemaker-accumulator model. The effects on the time perception caused by a high-arousal stimulus resulting in the emotion of fear can be explained through the experiments with neuroleptic drugs where the dopamine levels have been manipulated and the similar effects of emotion-induced time modulation were simulated.

The increased level of dopamine affects the clock block of the PA model, specifically pacemaker that increases the frequency the beats are produced with and it results in the speeding up of the internal clock, overestimation of time [6]. In other words, more pulses are produced by a pacemaker and accumulated in the same unit of time and this is perceived as if more time had passed than it actually had. The overestimation of time is achieved with a good accuracy explained with a framework of the Striatal-beat frequency model as well. As the SBF model works on the basis of cortical neurons oscillation, there is a proven influence of the dopamine release on those neurons´ activity [15,22].

This resulting overestimation of time may, in my opinion, from a psychological aspect give paradoxically more time for responding to stimuli. For example, when a human or an animal is feeling endangered, the fear results in an increased speed of the pacemaker and it could possibly give the animal a chance to act faster because of the feeling of having a subjectively shorter time for his reaction. However, we can argue whether there is any impact on a reaction speed as well.

I posit that the ability of time perception and the constant distortion of time perception could be evolutionary aspects - crucial properties of animals and human beings when it comes to self-defense. Time distortion could be theoretically underlying the ability to adaptively respond and adjust for the

stimuli experienced in our environment. Whether the feeling of a less time is enabling us to act faster is just a hypothesis that would, however, deserve further research.

8.3.1.1 Fear and its contribution to research

Besides the possible clarification of the time modulation, fear offers another navigation regarding neuroanatomy underlying the interval timing. It is believed that a good majority of brain structures involved in an interval timing has been identified. However, a recent study highlighted the need to examine another brain structure that has been long overlooked by researchers. Although its primary role might be considered as different, its importance to interval timing is obvious. Amygdala represents the structure of the brain being examined and the researchers have investigated the role of intra-amygdalar dopaminergic transmission in interval timing [101].

The experiment involved the injection of the D1 receptor antagonist (SCH23390) into the basolateral amygdala. The results affirmed that D1 receptors' dopaminergic transmission in the amygdala is involved in timing because when they blocked dopamine D1 receptors, the amygdala resulted in a modification of timing behaviour. The interval timing is processed by the activation of thalamo-cortico-striatal circuits that create a large network of areas in the brain including the basal ganglia and the prefrontal cortex [1]. The experimental data, therefore, suggest that the amygdala is involved in this network as well and its specific function would entail further investigation.

Emotions and the influence on interval timing models

	Attention	Arousal	Clock speed	Time experience	PA model	SBF model
Anger	Drawn to non-temporal stimuli	High level	Increased	Faster	Attention is drawn from timer, less pulses is allowed to pass to accumulator	Increased level of dopamine in a synapse resulting in increased clock speed
Fear	timer	High level	Increased	Faster	Attention is allocated to timer, gate is widely open	Increased level of dopamine in a synapse resulting in increased clock speed
Happiness	Drawn to non-temporal stimuli	High level	Increased	Faster	Attention is drawn from timer, less pulses is allowed to pass to accumulator	Increased level of dopamine in a synapse resulting in increased clock speed
Sadness	Timer	Low level	Decreased	Slow down	Decreased speed of the clock and attention is allocated to timer, fewer pulses accumulated per unit of time	Decreased level of dopamine in a synapse resulting in decreased clock speed, underestimation of time

8.3.2 Slowing down of time

Indeed, whenever people are experiencing some strong-emotive events or they are exposed to a threat, they often report time being perceived as slowed down in a retrospective judging of time. This specific modulation of perceived time may find its explanation in an enhanced pacemaker-accumulator model with an added attentional gate. And as prospective time judgments (information about timing prior the task) are highly dependent on attention and on arousal level, the AGM model is currently widely accepted [92]. In addition, there has been support provided for the AGM when it has been shown that high arousal and attention allocated to timing resulted in overestimation, thus the target duration was experienced as longer [93].

8.3.2.1 Skydiving

One of the studies that focused on fearful (high-arousal) experiences examined the case-study of skydiving. The participants in this experiment experienced the jump for the first time in their lives. Prior to getting on the plane, the participants received a questionnaire asking them to rate their level of fear and excitement for the upcoming jump. The time estimation in this experiment was retrospective, thus, they were asked to estimate their subjective experience of the duration of the fall only after the jump was finished. Based on other real-life experience, fearful events are associated with the slowing down of time. The same results were obtained even from this experiment and the level of fear was correlated with the time estimates. However, the jump was not considered as a significantly fearful, traumatic experience [94].

8.3.2.2 Footshock stress

Similar results can be observed even with animals such as rats when they were subjected to an electric footshock [36]. The footshock stress effect has a potency, similar to that of methamphetamine, to increase the release of dopamine in the brain, whereby the release is increased during high arousal events as well [95]. The Meck´s experiment (1984) [36] involved eight rats that were trained in a temporal discrimination bisection task with the short duration (2s) and the long duration (8s) under chronic footshock stress (0.2 mA). The test was held for 3 hours on selected probe days without the stressor. The results were then compared to the data obtained from a control experiment where the rats were trained without the stressor before being tested on selected probe days while receiving continuous footshock stress. These sessions involving receiving of electric footshocks were followed with another 3-hour long test albeit without footshock. The outcomes of these experiments showed that an electric footshock induces a leftward shift in a response to signal duration. However, when the continuous footshock stress is terminated abruptly, it results in a rightward shift. These findings offer

proof for footshock stress to cause an increase in clock speed as it increases the release of dopamine in the brain.

8.4 Facial expression effects on time perception

Different studies have focused on emotion-inducing through the presentation of emotional facial expressions. These experiments are based on the assumption of embodied emotions. This embodiment suggests the participant's adoption of the same emotional expression observed in another person. The observer is supposed to be experiencing the same perceptual, motoric and even somatovisceral states that an observed person is experiencing [96]. Niedenthal (2007) [96] mentioned that the principle that underlies this embodied emotions could be explained with so called "mirror neuron system", thus, there is a certain correspondence in the brain activity when the action is performed and when it is just observed.

This kind of experiment involves the presentation of, for example, 3 kinds of facial expressions (angry, sad, happy) and they are compared to one with a neutral expression [82,97]. In Droit-Volet experiment (2007) [21], the duration bisection task was used and the participants were trained to discriminate between two different standard durations. The short duration lasted for 400ms and the long duration for 1600ms. Subsequently, they were asked to classify presented durations that were in the form of faces with different emotions (sadness, anger, happiness) and a neutral facial expression to be more similar to the short duration or to the long duration. The results for the angry face in comparison to neutral facial expression showed a leftward shift of the estimated duration. In other words, the duration while watching the angry face was overestimated. Furthermore, the time overestimation was increasing with a longer durations spent watching the angry face that corresponds to a scalar property of the interval timing and it is consistent with an internal clock model that the lengthening of time estimation is an outcome of acceleration of pacemaker induced by a higher arousal level.

In general, threatening stimuli (e.g. angry facial expression) evoke a strong arousal response that may stimulate a rapid adaptive response and survival. The angry facial expression can have an effect on time estimation as it may indicate a threat of an attack and it may activate the defence system [21]. Therefore, this specific expression is more relevant to human perception and survival than other facial expressions [98]. Coupled with fear and its effect on the internal clock, it suggests a hypothetical explanation of an evolutionary importance of the time perception modulation for an individual's survival.

As it arises, the results from earlier discussed experiments offer an opposite behavior pattern, i.e. the high-arousal durations were overestimated compare to AGM. This inconsistency is trying to be interpreted by Tipples (2008), thus, duration overestimation results from a stronger effect of arousal rather than attention-based processes. That also serves as a support for arousal to represent an eminent factor in time modulation.

8.5 Methodological limitations

With regards to the experiments presenting facial emotion expressions, there is a question whether this type of experiment achieves the desired goal. There is no direct evidence if the facial emotion presentation induces the assumed emotions in the tested subjects, thus, the results from time discrimination tasks do not have to necessarily represent the emotional modulation of the perceived time. Although a theory of embodied emotions has been proposed, the presentation of an angry face is unlikely to produce the physiological response in a form that is similar to an emotion of anger. The presentation of an angry face is more likely evoking fear as the presented face may signalize a potential threat and thus, the arousal is being higher than for example while observing a fearful face that might present a threat just in an indirect form. Therefore, the experiments do not offer such informative value as expected.

To discuss the skydiving experiment, it does not offer satisfying results as well because of the duration estimation method. The method used for retrospective estimation is controversial in terms of its dependence on memory processes and it is very difficult to control the extent in which attention is paid to temporal information [99]. As a consequence of the shortcomings, the experiments should rather use the prospective time estimations to achieve the focus of attention on time. Indeed, some recent studies have already substituted this method and started to focus more on the prospective one [100].

Apart from previous experiments, a hypothesis has been proposed that the emotional modulation of time perception is not defined solely in terms of the level of arousal as has been earlier demonstrated. The data obtained by Tipples (2008) [98] have shown that the fearful faces were reported to induce the same level of arousal as angry faces but the overestimation was not so extensive as it was with respect to angry faces. Therefore, the initial prediction that the level of time overestimation is caused by negative facial expression is, however, dependent on individual differences in negative emotionality. The results supported the hypothesis stating that overestimation increases with negative emotionality as a strong positive correlation was observed between negative emotionality and temporal estimation variance due to both anger and fear. However, there was no positive correlation

in relation to happiness.

In summary, it is almost certain that emotions have eminent influence on time perception and all the experimental results are fairly consistent in reporting that emotions cause overestimation of the duration of emotional events. Nevertheless, nothing is flawless and even the most recent studies suffer from various methodological limitations. For example, when examining a change of certain time duration under the influence of a particular emotion, no control trials with non-emotional conditions that would confirm the exclusive potency of emotions for modulating the time have been performed. The suggestion would be to compare the temporal estimation of the emotional event to estimates of a neutral stimulus rather than to compare them with physical durations of time [73].

However, some other opinions have arisen suggesting that emotions may be simply a ´´by-product´´ of computations completed by other brain areas or that the time interval representation is an inherent property. This claim might be supported by evidence that the time-representing mechanisms are active even when timing is not required at all and this could theoretically give rise to the formation of many new specific timing mechanisms [102]. Another opinion that has been suggested in the twentieth century involves talks about the sense of time being grounded in our experience, this has been recently recommended to be reconsidered at a scientific level [78]. However, these assumptions are in the process of future investigation and when considering the evolution of the interval timing models. Despite their limitations, there are continuous efforts in enhancing their components. In addition, emerging new approaches could provide support for achieving further progress in this field via the creation of more ideal and accurate models. Thus, not being satisfied with the results obtained is the precondition of future success in any field of science.

9. Conclusion

Conceptualizing time as a fourth dimension is, despite the extensive research in this field, still an abstract notion for us. Nevertheless, there have been attempts to understand how the brain processes time. Creating timing models help us comprehend information that cannot be captured by any of our senses. The timing models discussed above indeed offer a very precise mechanism of how time is being processed and the observed physiological basics of its activity (e.g. dopamine, acetylcholine) resulting from the administration of pharmaceuticals or various kinds of drugs, and the brain structures included will serve as materials for further research. This thesis was substantiated with references made to both past and recent research, including reviews examining the relationship between time and emotions. Although some opinions might differ, I posit that the main factor of time modulation is not emotions per se but is instead the binding element connecting any distortion of time and emotions, the level of arousal.

10. References

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