Physiological Basis of Subjective Time:
Final Report for Nakayama Foundation for Human Science

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Time, intuitive and unintuitive

What is time? Time is intuitively obvious—you feel the flow internally. Albert Einstein changed this worldview with his theory of relativity, and made time as unintuitive as ever.

Time became one of the most fascinating and yet enigmatic topics through the Einstein-Bergson debate in 1922, where Einstein famously retorted, "*Il n'y a donc pas un temps des philosophes,*" that there is no such thing as philosophical time (Canales, 2016). Time did exist, according to Einstein, in physics and psychology as distinct entities. This statement was certainly disturbing to Bergson. For him, time could not be two things. Intuitive or unintuitive, time had to be a single entity.

Time enjoyed a special position in philosophy. Aristotle describes in *Physics* that time can be defined with reference to the perceived present moment *now*, which divides before and after (219 b 33-220 a 4). The now moment is completely subjective. Feeling the flow of time is the ultimate conscious experience. Your being aware always happens *now*, and it is *your* self-awareness. When you introspect, it is immediately obvious that the two are intertwined and inseparable. This idea of *now* fascinated many philosophers—and the idea has repeated reincarnations in various transmogrifications, probably the most famous version being Martin Heidegger's *temporality*. But before temporality, or maybe time consciousness, there was a word *durée*, or duration (Bergson, 1999). Bergson thought about *now* in practical terms. When you feel time, you feel the flux, the movement, which never is a frozen instance. But this is time that *you* feel, and you know it speeds up and slows down, regardless of how *I* feel about time, at the same physical time. I still remember one extremely long night when I was doing my first forced foot march in the army. It felt like several days, but it was only an overnight. That same exact duration of the night could have been an instant for someone who was preparing for an exam, or someone who was hosting a wedding reception.

Time that you feel subjectively is a *wagomu*, a piece rubber band. It sometimes stretches or shrinks. The span of your temporal *wagomu* is the extent of your free will. People who narrowly escaped a traffic accident often testify that right before the moment of collision, time froze and they could manipulate the handle in minute details, as if they wielded more freewill (Wittmann, 2016). Although Bergson probably had wanted to keep this special experience of time to be something unique and fundamental, this phenomenon is in many ways physiologically based. The subjective time dilation even has a name, called *tachypsychia*, and such state is well associated with epinephrine rush in the brain. The brain activity bursts in a concentrated timespan, and spares no time for the brain's time counter to tick. Neuroscience is in this sense a wonderful area to study, as it describes a dimension where psychological time meets physical time. But *tachypsychia* is really just a cheetah run. You cannot overdrive the brain all the time. There must be a physical and physiological limit that sets the pace of brain activity rhythms, and hence the pace of time, conserved universally across individuals sharing the same brain structure. Therefore, even though everyone appears to have a different span of subjective time in different instances (*durée* or temporality for that matter), we can still agree on how we feel about the general scale of passage of time.

Relativity of subjective time

While I was thinking about these issues, the Nakayama Foundation for Human Science made an interesting challenge to think about the *relativity* of subjective time. Small animals have faster heartbeat and shorter lifespan; larger animals have slower heartbeat, slower metabolic rate, and longer lifespan. Do the higher metabolic activities in the small animal mean in any way, that the small animal's subjective time would flow slowly, such that the total amount of subjective time is conserved across species? That is, would the one-year lifespan of a mouse feel like 60 years in a human? In Japanese folklore of *Urashima Taro* (浦島太郎), or Chinese mythology *Yu Xi Zhilin* (虞喜志林), a person makes a short visit to the world of gods and later realizes that he had actually spent a very long time in the human world. If the gods did exist (with extremely long longevity), these stories would be consistent with our observations so far.

The fact that time perception is physiologically based applies not just across species but also in aging individuals. We all remember that when we were younger, time flowed extremely slowly. Thirty years ago, I was sure that the sun will continue to rise and set in its own schedule, and leave me alone in my teens. Then I do not remember how I have got past my thirties and suddenly became someone in mid-forties. Psychologists give us good explanations on how this perceptual time warp happens. You do not count repetitions of daily routines in your accumulative account of time; as you get old, most of what you do becomes *SAMO*, or same-old-shit, which disappears from your chronological log. There are studies that suggest for a genuine change through aging in the scale of time perception, although the results are not so clear-cut. Like an old, stretched *wagomu*, our older self might find the extent of *durée* stretched in time, such that elapsing of physical time feels to occur much faster. This is difficult to verify directly. In the physiological level, on the other hand, there are some correlates of these observations: similar to the small and large animals, our maximal (and intrinsic) heart rate and basal metabolic rate decline gradually with age.

Physiological rhythms underlie subjective timespan

This brings us back to the original question on the relationship between subjective time and rhythmic physiological parameters. By definition, it is impossible to put *subjective* time on an objective timescale. Nonetheless, we can measure physiological parameters that underlie time perception in an individual level. The scale of time perception is seconds to minutes, while the timescales of physiological rhythms are much longer: most commonly ~24 h, known as the circadian rhythms. The scales of period itself do not directly correlate; but they do correlate if you look at the phases of time. Dopamine is the key neurotransmitter that makes you underestimate time intervals (Meck, 1996). **Figure 1** illustrates a schematic choice response trend under dopamine receptor agonist (red) and antagonist (blue) compared to control (gray). Under dopamine agonist administration, subject underestimates the passage of physical time.

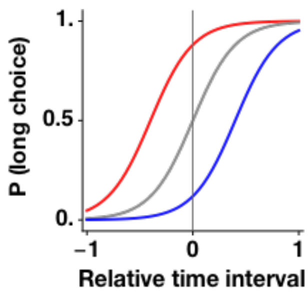

Figure 1. Dopamine distorts subjective estimation of time interval.

This provides an interesting clue to connect time perception with physiological circadian rhythms. For example, tyrosine hydroxylase (TH), the key dopamine synthesizing enzyme, shows circadian profile of expression in the brainstem (Chung *et al.*, 2014). The TH production is linked to the expression peak of a circadian gene *Rev-erba*, which is a part of the *Bmal-Rev* loop recently modeled in our own collaboration study, partially supported by Nakayama Foundation for Human Science (Schmal *et al.*, 2019; available at biorxiv.org). The data indicate that the peak phase of dopamine production must occur in the morning, and the trough should occur in the transition between day and night (**Figure 2**). In fact, people usually feel that time flies in the morning, and that we often say "Oh, it's already time for lunch," but we rarely say the same for dinner.

Dopamine is also a key neurotransmitter that underlies psychological modulation of motivation and mood. This makes sense because subjective time does relate to mood: my long night in the army camp was also a depressing night, while someone's night at wedding reception must have been an exciting one.

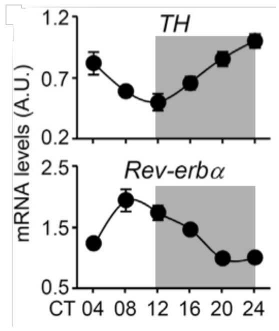

Figure 2. Brain's dopamine production (*TH*) is linked to the molecular circadian clock (*Rev-erba*). From Chung *et al.*, 2014.

Subjective time and mood, through seasons

Measurement of time perception is difficult to conduct in mice. Instead, mood state can be measured using a standard behavioral test such as the tail suspension test (TST) (**Figure 3**). Like time perception, mood changes as aging progresses. The dopaminergic system in the brain weakens through aging, and a tendency towards depression occurs in our later lives. A longitudinal tracing of mood through a lifespan would take a too much time to conduct. Even a common laboratory mouse has a longevity span of about 2 years. Would there be a physiological rhythm span that is experimentally more practical yet theoretically meaningful?

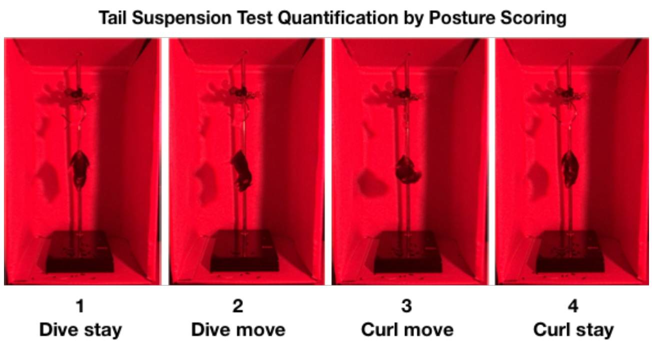

Figure 3. Tail suspension test and basic posture scoring.

Physiological rhythms comprise many timescales: from shorter than 24-h period rhythm called ultradian rhythm to longer than 24-h period rhythm called infradian rhythms. We are covering all of these scales, and a circadian-ultradian rhythm study we performed through an international collaboration is now under submission (Chrobok *et al.*, 2019). We initially focused on the infradian rhythms of estrous cycles, occurring with a 4-day period in female mice. The computational modeling is still on going, but experimental validation process turned out to prolong. We therefore sought alternative infradian paradigms, and found the seasons of summer and winter to be an ideal timespan to look at.

We performed TST longitudinally over a 24-h cycle in 4 mice under summer (16-h day and 8-h night) and in 4 mice under winter (8-h day and 16-h night) day-lengths, simulating the seasonal light-dark conditions in Northern European cities. We quantified the mood state of a mouse by posture scoring, in the order from demotivated to motivated states (**Figure 3**). The result came out quite clearly the morning-midday peak in the posture score (**Figure 4**), correlated with the expected hindbrain peak of dopamine production (**Figure 1**). There also was a seasonal difference, with higher motivation to resist from tail suspension in summer (long day, LD) than winter (short day, SD) (**Figure 4**, rightmost panel).

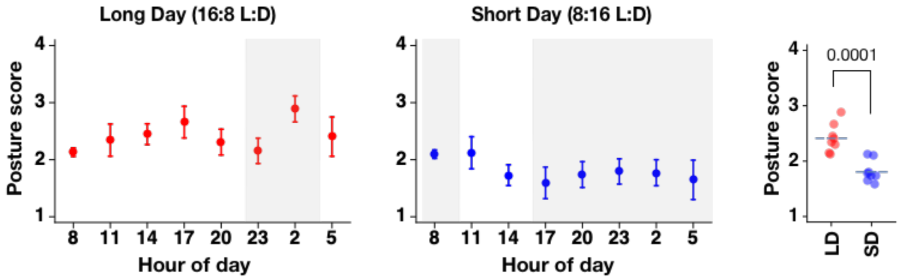

Figure 4. More active posture state observed during summer (long day, LD) than winter (short day, SD). The posture state dips to a demotivated state at the transition point between day and night (unpublished data).

What are the neural correlates of these mood changes, which potentially reflect changes in time perception? To find out, we have constructed by hand a machine to visually observe circadian gene expressions *in vitro* (**Figure 5**). The system performs real-time measurement of bioluminescence intensity from luciferase-fused clock proteins that are expressed rhythmically by cellular circadian clocks. We are still working on identifying the correct brain loci to observe.

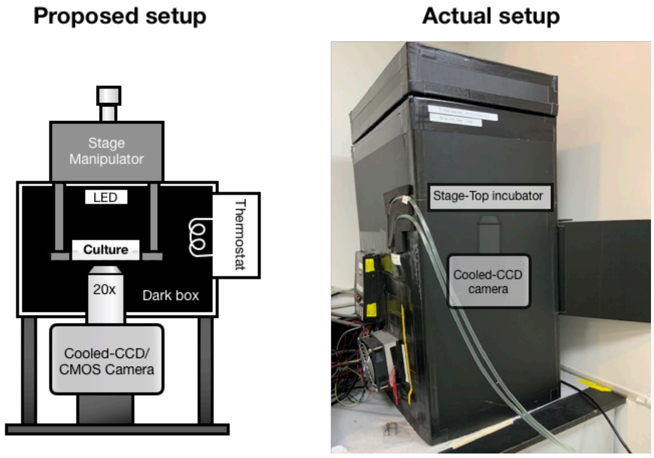

Figure 5. Imaging setup partially financed by the Nakayama Foundation for Human Science.

Time in the sick body

In the meanwhile, we targeted at circadian clock tissues in the brain and the body that are easier to target. Our own previous work showed that the circadian rhythm accelerates during the summer and decelerates during the winter (Myung *et al.*, 2015). This finding correlates with our observation that the mice are more excited during the summer than winter (**Figure 4**). Similarly, when we are sick, we are depressed.

The kidney harbors a very robust clock, second only to the liver circadian clock outside the brain. The kidney clock is easy to prepare and is anatomically and physiologically clearly defined. We therefore induced a disease state called chronic kidney disease (CKD) by adenine feeding and observed if the circadian period increases, as in the winter condition. This apparently simple experimental paradigm proved to be not so simple. The animal developed unstable behavioral circadian rhythms (quantified by period standard deviation, period SD), but it did develop a longer period at the end of adenine diet. The animal was generally sick and preferred to stay in the resting position, making TST an impractical experimental test. However, we did find something quite interesting and perplexing. The mice suffering from CKD had the intact "master" circadian clock, the suprachiasmatic nucleus (SCN), which regulates the sleep-wake cycle in this species. The answer to this mystery lied in kidneys. The CKD kidneys expressed longer circadian period rhythms with unstable rhythmicity (characterized by higher period SD). These observations led us to believe that the kidney clock can feed back its aberrant clock signals to the SCN and affect the behavioral circadian rhythms under disease states (**Figure 6**). This work, which is the first experimental work from our laboratory and also a result from an international collaboration will be published soon thanks to the partial financial support from the Nakayama Foundation for Human Science (Myung *et al.*, 2019).

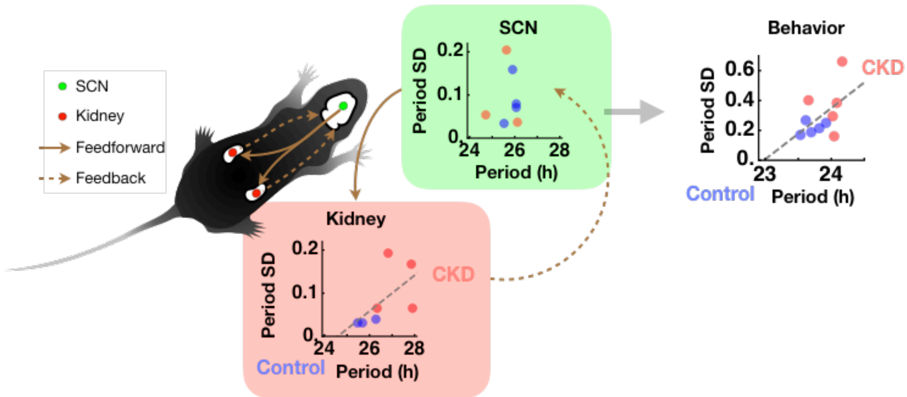

Figure 6. Distributed physiological timers, for example, the kidney circadian clock, and their feedback to the main clock, the suprachiasmatic nucleus (SCN). Adapted from Myung *et al.*, 2019.

Onward: subjective time and physiological rhythms

The best questions are often philosophical. But the best answers are mostly scientific. Questions about time, both subjective and objective, touch upon the fundamental domains of our lives and our worlds. To pursue these questions, I opened a lab called "Laboratory of Braintime." A novelist Carey Harrison—we ran a "consciousness club" in Berlin—suggested the name for me. I predict the best answer to questions on subjective time will come from neuroscience. Multiple scales of physiological rhythms modulate mood and time perception at their own respective level. The overall structure is almost fractal (**Figure 7**).

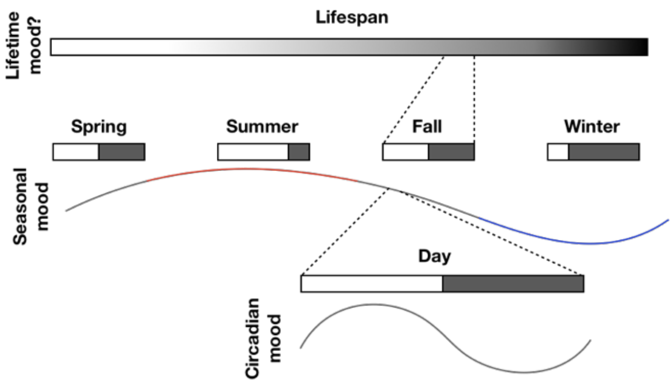

Figure 7. Fractal structure of mood, from circadian cycles through seasonal cycles to a life cycle.

With the partial financial support from the Nakayama Foundation for Human Science, we could purchase critical components for constructing the bioluminescence imaging setup (**Figure 5**). The support helped us produce three pending publications (Schmal *et al.*, 2019; Chrobok *et al.*, 2019; Myung *et al.*, 2019) that are expected to appear this year. I am especially proud of my laboratory members, a research assistant Chun-Ya Lee from Taiwan, a graduate student from Amalia Ridla Rahim from Indonesia, a graduate student and an MD Vuong Hung Truong from Vietnam, for the progresses that we made together to get here. I thank all of them, and I thank once again the Nakayama Foundation for Human Science for the generous support and for the excellent question on subjective time.

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