From Department of Neuroscience
Karolinska Institutet, Stockholm, Sweden

Neural circuitry mechanisms in decision-making

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Stockholm 2017

The cover is illustrated by Yun Lan 蘭韵

Published by Karolinska Institutet.
Printed by AJ E-Print AB

ISBN 978-91-7676-640-8

Neural circuitry mechanisms in decision-making

THESIS FOR DOCTORAL DEGREE (Ph.D.)

Academic dissertation

Public defence at Samuelssonsalen, Tomtebodavägen 6,

Karolinska Institutet, Stockholm, Sweden

Friday the 28th of April, 2017 at 9:00

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Abstract

The brain is the exclusive organ that makes decisions for humans and the society. In this thesis, I will discuss recent advances in the understanding of neuroscientific mechanisms in decision-making. Decision-making is not a new topic in the human history, but it has existed for thousands of years. We made numerous decisions over centuries, and the consequences of those decisions transformed the landscape of the Earth, established the norms for our society, and revolutionized our way of thinking. To understand the concepts and frameworks for decision-making, I will review significant intellectual advances in the history, start with several simple enough models to describe and predict decision-making behaviors. However, the models, concepts, and logical deduction do not provide enough understanding of the decision-making process. We should also aware limitations, which determine our choice processes and outcomes, such as how much information we have, how much cognitive power we can put into a problem.

After the established the models that sufficiently contain the errors and limitations of decision-making, the central question is to understand the brain, which operates the whole process. As the brain is specialized into functional regions, it is easier to build hypothesis in decision-making process if we conceptually break down the decision-making process into discrete stages. Firstly, attention is the foremost important mechanism controls our actions and choices. Only with attention allocated to the problem, one can then represent the problem to related brain areas, mobilize memory and the affective system to retrieve internal status, start evaluating different choices, plan and take action, reevaluate the outcome and update the original memory and representation of values. To further dissect the decision-making mechanism in the brain, particularly in this thesis, we examined and discussed neural circuits that are regulated by local interneurons and long-range neuromodulators. Moreover, such knowledge can be robustly translated into an understanding of various types of mental disorders. In this thesis, three studies are included to illustrate how different neural circuits could alter animals' decision-making process and performance.

In Paper I, the prefrontal fast-spiking interneurons were recorded and manipulated in a task measuring a goal-directed behavior and top-down attention. The neuronal activities of fast-spiking cells in the medial prefrontal cortex were significantly regulated during the attentional process, and such pattern defined the firing of the principal neurons with a phase-locking mechanism. We further showed enhanced gamma synchrony characterized the successful allocation of attention. Moreover, modulation of gamma

synchrony using optogenetics can significantly change the animals' performance in top-down attention. In Paper II, we investigated the functions of fast-spiking NMDA glutamate receptors in depressive-like behavior. Using a genetically modified animal model, we compared the phenotypes between the fast-spiking NMDA receptor knockout animals and controls. There was no significant difference between two groups in response to non-competitive NMDA receptor antagonist in expressing depressive-like symptoms or in anhedonia. In Paper III, we investigated the role of the long-range modulatory serotonergic system in impulsive behaviors. Activation of the ascending serotonergic population with optogenetics slightly alleviate the level of impulsiveness in both impulsive action and impulsive choice. Conversely, optogenetic inhibition of the ascending serotonergic population significantly increased impulsive action and impulsive choice. Furthermore, using optical calcium imaging, our results illustrated that the neuronal activities of the ascending serotonergic population strongly responded to the delivery of reward. In summary, the work of this thesis provides a further understanding and new insights of functional roles of particular neuronal subpopulations in different discrete stages of decision-making.

LIST OF SCIENTIFIC PAPERS

I. Hoseok Kim, Sofie Ährlund-Richter, **Xinming Wang**, Karl Deisseroth, Marie Carlén
Prefrontal Parvalbumin Neurons in Control of Attention.
Cell. 2016 Jan 14;164(1-2):208-18.

II. Laura Pozzi, Iskra Pollak Dorocic, **Xinming Wang**, Marie Carlén, Konstantinos Meletis
Mice Lacking NMDA Receptors in Parvalbumin Neurons Display Normal Depression-Related Behavior and Response to Antidepressant Action of NMDAR Antagonists
PLoS One. 2014 Jan 16;9(1):e83879.

III. **Xinming Wang***, Daniel Kaping*, Marc Parent, Iskra Pollak Dorocic, Hester Meeusen, Daniel Fürth, Konstantinos Meletis, Marie Carlén
Serotonergic neurons directly control impulsive behaviors in rats.
Manuscript

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List of abbreviations

ACC	Anterior cingulate cortex
ACh	Acetylcholine
AMYG	Amygdala
BF	Basal forebrain
CSF	Cerebrospinal fluid
DA	Dopamine
dlPFC	Dorsalateral prefrontal cortex
DRN	Dorsal raphe nucleus
DSM	Diagnostic and statistical manual of mental disorders
DPSS	Diode-pumped solid-state laser
fMRI	Functional magnetic resonance imaging
FS	Fast-spiking
FST	Forced swimming test
GABA	*gamma*-Aminobutyric acid
GPCRs	G-protein coupled receptors
HPC	Hippocampus
ICD	Classification of mental and behavioural disorders
IL	Infralimbic cortex
IR	Infrared
ITI	Inter-trial interval
LDTg	Laterodorsal tegmental areas
LED	Light-emitting diode
LHb	Lateral habenula
MFB	Medial forebrain bundle
mPFC	Medial prefrontal cortex
MRN	Median raphe nucleus
NA	Numerical aperture
NAcc	Nucleus accumbens
NIMH	National Institute of Mental Health
NMDAR	*N*-methyl-D-aspartate receptor
OFC	Orbital frontal cortex
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
PPTg	Pedunculopontine tegmental areas
PrL	Prelimbic cortex
PV	Parvalbumin

RMTg	Rostromedial tegmental nucleus
SEU	Subjective expected utility
SMA	Supplementary motor area
SNc	Substantial nigra pars compacta
SNr	Substantial nigra pars reticulata
SPT	Sucrose preference test
SSRI	Selective serotonin reuptake inhibitor
SST	Somatostatin
TMS	Transcranial magnetic stimulation
VIP	Vasointestinal peptide
vlPFC	Ventralateral prefrontal cortex
vmPFC	Ventralmedial prefrontal cortex
vStr	Ventral striatum
VTA	Ventral tegmental area
3-CSRTT	3-choice serial reaction time task
5-CSRTT	5-choice serial reaction time task
5-HT	Serotonin, 5-hydroxytryptamine

"We must know. We will know."

David Hilbert

1 Analysis of Decisions

1.1 Introduction

In 1900 David Hilbert, one of the greatest mathematicians, published 23 in-depth crafted problems, known as Hilbert's Problems, which were all unsolved then. These problems are still the most deeply considered problems ever generated by a single person, most of them were inspiring although they were daunting at that time and continue to be so even today. Later many problems from his collection decided the course of the mathematics research in the 20^{th} century. Until recently, we have only successfully solved half of the problems. As Hilbert said, *"Wir müssen wissen — wir werden wissen"*, we set off with a vision to conquer unsolvable, although we often fail along the course, our collective actions will eventually take us to success.

Nevertheless, how can we human achieve long-term success given we may fail with a much higher chance? How can we continuously push the boundary of our wisdom, knowledge or technology? If we take a close look at our biological composition, the human is neither the strongest nor the fastest species on the Earth. We don't have large brains or sharp teeth. We are vulnerable to what nature brings, like temperature, oxy-

gen, bacteria and countless more. Nonetheless, the most extraordinary human ability is rational reasoning which we are most proud of. The human brain has not been changing its function very fast over centuries. How can we still function in a highly complex and demanding society today when are still using functionally the same brain as our ancestors' thousands of years ago.

One of the fundamental power of the human brain is that our ancestor made decisions with long-lasting effects, which determined how the world would look like, and we will make decisions that have impacts on generations of people in the future. The French philosopher Albert Camus said *"Life is the sum of all your choices"*. But he was only right for the first half. Our imagination, collective behaviors, especially our decisions, in cumulative actions not only shape us from the past to future but also horizontally transformed landscapes on the planet, developed the social order, justice, commerce, even our ways of communication. So we could create comfortable homes, the young and sick ones are taken care of, and we can easily connect with family or friends on the other side of the planet. It is because of our collective wisdom, cumulative decisions and actions made us the first species on the globe that break the genetic code of the carbon life form, created silicon-based intelligence and even mastered the technology to leave the planet.

With the advances in technology and innovation, we are already living in a completely different environment compare to our ancestors. We no longer need to worry about predators like lions or wolves, and our crops are better protected from drought or flood than ever. However, some of the ancient instincts and mechanisms of survival in the brain are still playing a significant role in our decision-making processes, therefore influence our daily lives. Moreover, we're facing a more pressured situation in making decisions because of time limits, shorter attention spans, conflicts of information and overload of choices. For example, when we drive a car, messages or phone calls will drain our attention and make it extremely tough to make a right decision when we encounter some emergency situations. Sometimes even for the simplest task as grocery shopping, we get very confused when we face several dozen varieties of different brands of jam.

There are many mental shortcuts people usually take for decision-making. Rule of thumb is the most common one, it is reasonably effective and gives little mental burden to a decision maker. Although it can be mindless sometimes, surprisingly it works well when we do grocery shopping or dining in a restaurant, and even if it was a bad choice, the cost is low enough not to cause any harm to us. However, it can be very costly when we need to consciously make decisions regarding risks in stock market trading, life insurance, or about the choices which their outcomes can only be realized in the future with a temporal gap, such as investment in the pension. Our biology was not designed to handle questions like such, and our ancestors rarely had to deal with those problems. As our civilization evolves and more complexity being continuously added to our life, some people realized we need to understand the process and mechanisms of decision-

making, and also be able to make optimal choices eventually.

We spent thousands of years developed and practiced thousands of ways of making good decisions. In Chapter 1 I will discuss how this issue evolved over years and examples of modern decision analysis methods, which will also put many concepts and rationales in context. As we don't take Rome was built in one day. Instead, it took us more than 2000 years to shift our decision-making strategy away from consulting stars and magic. It took another century for us to build scientific theories and methods as the basis for rational decision-making. We are also getting better at realizing limitations in our reasoning and approaches in the past century, so we don't confine ourselves in the existing frameworks and logic. Modern analysis of decision with mathematics are challenged in many ways especially in the field of psychology, as human or animals tend to rely heavily on the ancient built-in mechanisms in the brain, we make thousands of mistakes in our decisions that against our economic interest. Those errors and biases generated along will be discussed in Chapter 2, so we can be aware of the limitations or pitfalls from a view of a single research field. Nowadays, decision-making has already evolved to combine the fields of mathematics, sociology, psychology, economics, political science, and neuroscience.

In Chapters 3-5, I will discuss the neuroscience of decision-making. After all, it is the brain came up with all the beautifully constructed tools and frameworks to help our decision-making process, it is also the brain that makes all the mistakes over and over. As it was mentioned earlier, it is hardwired to solve short-sighted, imminent problems, and neuroscience will give the answer about how it is wired to be impulsive and to perform simple tasks, or what is the mechanism to overcome the impulsiveness? In Chapter 3, a useful conceptual framework will be used to break the decision process into smaller components, which can be tested individually in experimental settings. In Chapter 4 I will discuss the neurons as building blocks of the whole complex machinery, and discuss abnormal decision-making functions related to psychiatric dysfunction of the brain in Chapter 5.

In the last two chapters, I will summarize the findings in this Ph.D. thesis, focusing on how the brain overcome the built-in impulsive mechanisms at different levels. Using methods like optogenetic and optical imaging, we can dissect specific circuits of the brain that control attention, emotion, or impulsiveness. Targeting the brain in ourselves, improving our capability in problem-solving and decision-making, will not only benefit daily lives, school or career choice of individuals but also improve the decisions and well-being of the whole society where decisions are inevitably required. Many organizations or activities such as nationwide health care system, international consortium against poverty or diseases, management of earthquakes or tsunami, will benefit from it. With the help of knowledge in economics, psychology, mathematics, computer science, the research of neuroscience holds a new promise of transforming our society for better dealing with the key issues and decisions in a new way.

1.2 Lessons from history

Today, the human is facing greater uncertainty than ever in our lives and we have much less time, with some even down to seconds, to make a choice. On the other hand, we have accumulated a significant amount of knowledge and insights regarding decision-making from thousands of years of practice and failures. Some of the knowledge and insights are outdated, but many of them are still in use today. One question is, to know how good are these methods? Humans are good at learning from past failures, so what can we learn from our ancestors? To answer this question, let's take a look at how our ancestors made decisions thousands of years ago when people sought out guidance and hints from stars, augury, magic and traces from nature.

During the Shang Dynasty (1600 BC - 1000 BC) in ancient China, kings consulted shamans to receive messages from the high god, and then they decided in which direction the army should head, or how many slaves should be sacrificed, as the high god himself planned an action. The shamans held the secrets of communication between humans and heaven. They performed a ritual where they burned turtle shells, or "dragon bones". They carefully listened to the sounds of the shell cracking and interpreted the patterns the fire left on the shells. Something useful came out of these cracks; they were used to develop the written characters of the Chinese language (**Figure 1.2.1a**).

I Ching, the "Book of Changes" is full of poetic language and arcane knowledge wrote from a wise king. It became the ultimate guide for Chinese in daily lives, especially for the lords (1000 BC - 750 BC). The Yin and Yang from Tai Chi were derived into sixty-four hexagrams, formed a circle symbolize the heaven and square as the earth (**Figure 1.2.1b**). With some spiritual practice as well as a profound understanding of the cryptic language, a few wise men were able to use it for predicting the future. One of the greatest poets and a king locked himself in the sacred cell and tried to reveal the truth of the universe by studying I Ching, while his enemy had more than one hundred thousands troops surrounded his capital. Either this book failed him, or he failed to get the ultimate truth, and he was captured and lived a tragic life afterward, however, created even greater poems in the rest of his years.

Delphi, the center of the world, where two gold eagles met representing order from Zeus. In ancient Greece, Delphi represented the ultimate decision mechanism during 800 BC to 400 BC. And Pythia, the priestess in the Oracle of Delphi performed mythical rituals to predict the future (**Figure 1.2.1c**). Supplicants often undertook long journeys to the oracle to seek counsels from Apollo. So as to get guidance from the oracle, they were to be interviewed, and their cases were to be framed. Moreover, they had to present gifts. On a day without bad omens, a supplicant would be led into the temple, to the seat of Pythia. There, he or she would receive his/her answer in the form of poetic hexameters and then leave for home. Of course, as the guidance related to the foresight of the future, the supplicant knew he or she should follow

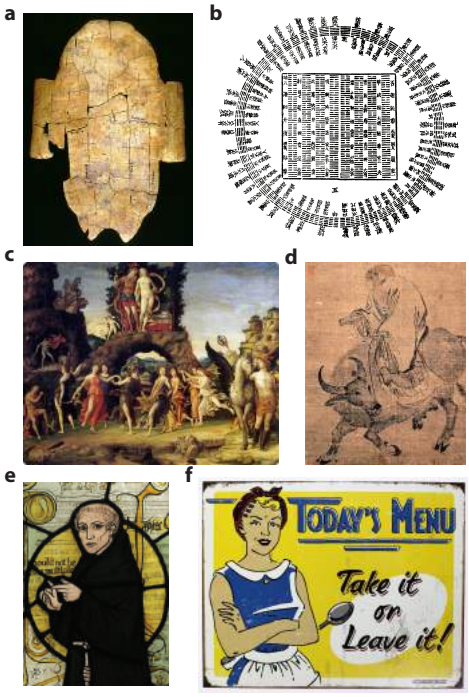

Figure 1.2.1: **a** Augury from Shang dynasty 1600 BC - 1000 BC China. Shamans put turtle shells on fire and then study the cracks to send High God's information for the kings to make a decision. **b** I-Ching, the "Book of Changes" in China 1000 BC uses Yin and Yang to derive hexagrams to predict future. **c** Oracle of Delphi in ancient Greece. The priestess in the Oracle gave guidances to supplicants for their hard life choice. d, Lao Tzu proposed to make decisions with the minimum human will and be spontaneous. e, Ockham's Razor, as rule of thumb is still the most commonly used decision-making approach. **d** Hobson's Choice, as the choice proposed where no real alternative is given.

it and confirm the consequences.

Lao Tzu (700 BC, **Figure 1.2.1d**), on the other hand, proposed an entirely different way of making decisions. He argued for being in harmony with the Tao. Thus, a human should make a decision with a diminished will; that way, he or she could achieve spontaneous actions and choices, and doing so should cost no effort in the brain. In such a purely natural way of behaving, one can imagine the flowing of countless lives like a river running effortlessly into the sea; however, this way possesses enormous power, much like water's ability to break even giant stones. On the contrary, if one were to make decisions or actions without the natural intention of the Tao, nature would lead matters to the opposite consequence. Besides, the society should also follow the ways of nature and natural creation and have only minimal rules or regulations so as to keep the purity of the community.

During 500 BC to 300 BC, the city of Athens developed an entirely different way of organizing their society and making decisions. As Aristotle described, people administered all business through decrees (assembly) and law-courts. Issues such as military, financial, and diplomatic decisions were freely discussed, debated, and later decided by voting by all male citizens who owned land. Also, the assembly monitored the decisions to be enforced, and the staff performed its duties correctly. This process undoubtedly took more brainpower, and we are still practicing decision-making in a similar way. However, we usually cannot

be sure if it the best option was chosen. In 399 BC, the citizens of Athens convicted Socrates of corrupting young people and failing to acknowledge the gods; they later put him to death by poisoned hemlock.

One widely used and still very effective way of making decisions is heuristic, or the rule of thumb. This approach facilitates a fast process and provides a minimal sufficient solution to immediate goals. The success of making decisions using heuristic relies on one principle, Ockham's razor (**Figure 1.2.1e**). The principle essentially states that the best theory is the simplest one that accounts for all the evidence, so that unnecessary items or similar conclusions will be cut off from hypotheses or actions. As John Punch formulated the in 1639, *"Entities must not be multiplied beyond necessity"*, the simpler theories and methods are favored and selected based on this principle. We should also note that this principle doesn't necessarily make complex models wrong. Instead, complex models are harder to be verified with scientific methods. As Isaac Newton explained, "We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances."

In the 16th century, a stable master Thomas Hobson in Cambridge, England found people always picked the fastest horse from his stable, which made the popular horses overloaded and weary. Then he came up with a brilliant solution by presenting the following free choice to his customers. He showed the customer the horse that was standing closest to the door, and ask his customer to either take this one or no one. And later Hobson's choice became the term widely used and misused, but it essentially describes the free choice but no alternative situation where people have to choose between something or nothing (**Figure 1.2.1f**). Henry Ford presented the same choice to his customers: "Choose any color you like, so long as it's black." In the 1980s, the decision was formulated as the "ultimatum game" and studied systematically.

We sometimes encounter more challenging situations than Hobson's choice. Hamlet, in Shakespeare's book, wondered, "To be, or not to be: that is the question." In that scenario, he had to compare the pain of life with the alternative, but he was unsure of and dreading about death. He had an important insight, namely that no one came back from death; so, the consequences, whether they involved reward or suffering, could not be discovered. That decision was not reversible; there was no way back, so it put him in a tremendous dilemma. Many years after the problem, with a bottom-up approach to generalizing theories from quality facts, Francis Bacon argued inductive reasoning was a superior method. In the Cartesian rational world, René Descartes opened a new horizon of scientific research; he argued reasoning was the superior power that set humans apart from animals. Having acquired a "scientific method," he established that observables no longer restrained us; instead, we entered the era where we can explore the world that we can neither see nor feel.

1.3 Classical decision theories

1.3.1 Subjective expected utility theory

Certainly, despite a large number of obscure names or abstract concepts that we generated so as to describe decision-making processes, everyone is practicing his or her decision-making capabilities in everyday life without much trouble. Moreover, weighing up costs and gains or reflecting on future consequences is a painless matter for us. For example, a person goes to a supermarket to do some grocery shopping, and he or she finds that three oranges cost as much money as two chocolate bars (**Figure 1.3.1a**). How should the person decide, given that the monetary values are the same? If one has a strong preference for chocolate, this decision process would probably take less than one second. As Daniel Bernoulli stated more than 200 years ago, "The price of the item is dependent only on the thing itself and is equal for everyone; the utility, however, is dependent on the particular circumstances of the person making the estimate."

Clearly, even if different goods have the same monetary value, they most likely have different values to each person, and such values cannot be directly observed or measured. Therefore, to overcome such difficulties, utility is used instead of preference when making decisions regarding certain goods. Additionally, the concept of utility can be expanded to measure not only preference for goods but also preference for different jobs, services, information, etc. (**Figure 1.3.1b**). Utility represents the overall satisfaction that one experiences after consuming certain goods or services, with the constraints of price and income. A common way to visualize the preferences is the indifference curve, that is a graph also used in microeconomics with applications to understanding demands. Basically, an indifference curve plots each points where the utilities of x amount of goods/services X, and y amount of goods/services Y are indifferent for one person. Then by exploring different combinations of X and Y, we will be able to draw an indifference curve (**Figure 1.3.1c**).

An interesting attribute of utility is that it does not increase linearly with the increase in amount. For example, buying 10 chocolate bars would not generate 10 times the satisfaction as from buying 1 chocolate bar. Instead, the increase of satisfactory experience drops down as the number of goods increases. The same principle applies to services as well, for example, watching six hours of a movie probably won't generate three times the pleasant experience of watching a two-hour movie. Sometimes, the utility might even go negative. This can be measured as the difference of utilities while changing the number of goods or services, with a term called diminishing marginal utility (**Figure 1.3.1d**). Formally, the utility function can be defined as $u : X \to \mathbb{R}$, where X is the set of goods or services; the function u produces a real number. Using the concept of diminishing marginal utility, we can compare people's preferences mathematically.

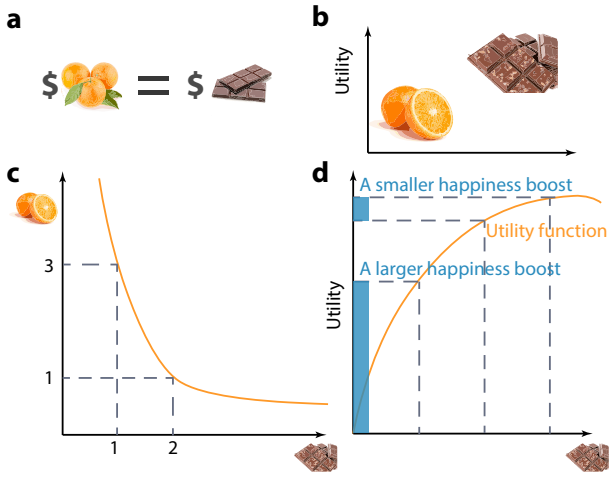

Figure 1.3.1: **a** Monetary comparison, 3 oranges and 2 chocolate bars have the same money value. **b** As each item gives different subjective reward or emotions to individuals, items often exhibit different utilities. **c** Indifference curve measures the points where combinations of quantity and item make indifferent utility to one person, in this case, 3 oranges plus 1 chocolate bar has the same utility as 1 orange and 2 chocolate bars. **d** Marginal utility diminishing illustrate the non-linear relationship with the total utility of one item and its' quantity. For every new item acquired, the utility added is decreasing, and for some items, adding new item could reduce total utility.

Using the previous example, now we have $u(\text{nothing}) = 0$, $u(1 \text{ orange}) = 2$, $u(2 \text{ oranges}) = 3$, $u(3 \text{ oranges}) = 3.5$, $u(1 \text{ chocolate bar}) = 2.5$, $u(2 \text{ chocolate bars}) = 4$. Then, by comparing the numeric values of an item's utility, we know this person prefers two chocolate bars over three oranges.

Another challenge is that, under many scenarios, we will, unfortunately, have a hard time knowing when one event will happen or how likely it is to happen at a certain point in time. The utility function generated above is suited for a static situation where all conditions are displayed. Moreover, the individual who will make the decisions needs complete information. In a dynamic and uncertain environment, people will have difficulty judging utility or preference. In the old days, people sought ways to solve this problem. For example, in Greek mythology, Zeus, Poseidon, and Hades divided the universe by rolling a die, as there seemed no fairer way. The lucky ones got the sky or the ocean, but the unfortunate one got to rule the underworld. In our daily lives, chances or risks are inescapable. There are chances that public traffic is running late. One may accidentally discover some favorite songs or fall on the slippery ice during winter. Although many events have relatively low risks and low chances of happening, their accumulated consequences become an avalanche of events with a greater cost. In contrast to the attempts of controlling events and their trajectories, which human species still doesn't know how, it is more reasonable to manage risks with some reliable frameworks.

One of the first people who studied the risks was an Italian mathematician who tried to solve the famous "problem of points" during da Vinci's era. In this problem, two teams play a game, and each goal gets 10 points. The team who gets 60 points wins the game. However, sometimes the game is interrupted, and people have a hard time judging who could win if the game resumed or how to divide the prize if the game could not be resumed. It was not until 1654, after many letters were exchanged between Blaise Pascal and

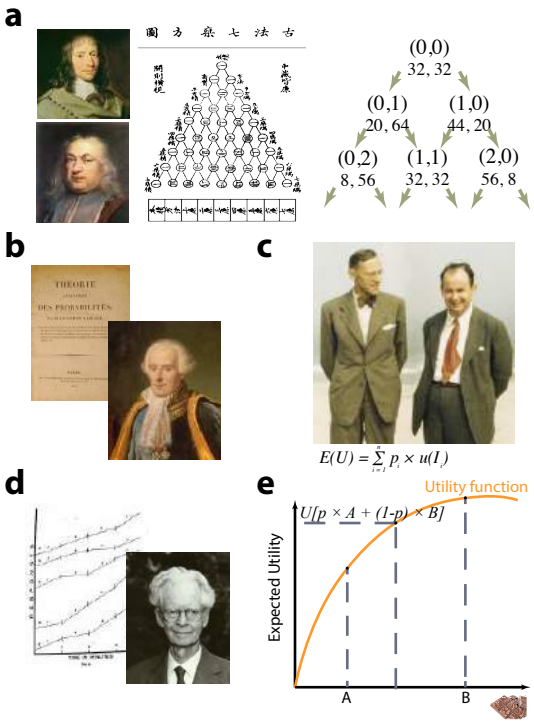

Figure 1.3.2: **a** Pascal, Fermat and Jiaxian's Triangle as the first rational way of solving expected future values. **b** Laplace laid the foundation of statistical analysis with his article. **c** Morgenstern and Neumann developed the expected utility theory in 1947. **d** BF Skinner used the frequency of response to measure subjective utility from animals, **e** Non-linear (concave) expected utility function. With increase of quantiy, the utility decreases, therefore, expected utility of quantity A happening with probability *p* and quantity B happening with probability *1-p* predicted by Morgenstern-Neumann's theory is smaller than actual utility.

Pierre de Fermat, that they discovered the rational way of dividing the prize fairly and laid the ground for one of the most influential theory. For simplicity, we assume that the prize is 64 units of goods, and for each round, both teams are equally skilled, resulting in a 50-50 chance of getting one more goal. In the figure, (A, B) represent how many goals team A and B get at certain stage (**Figure 1.3.2a**). Stages are represented as the layers of the triangle, so as the game move on, the numbers move one more layer downward. In the number below the bracket, are how the 64 units should be divided. By calculating how much one team was expected to get based on the current state and chance to make a goal or not, the expected value was given birth as well as probability theory. The same triangle idea was also found in Song dynasty in China in 11^{th} century.

In 1738 Daniel Bernoulli published his famous paper *"Exposition of a New Theory on the Measurement of Risk"* laid the foundation for analysis of risk aversion and utility. Pierre Laplace in 1812 published his work *"Analytic Theory of Probability"* significantly advanced the probability theory and therefore analysis of risk (**Figure 1.3.2b**). In 1921, American economist Frank Knight proposed a distinguished concept between risk and uncertainty for being knowable or unknowable respectively. As it is clear that risk is measurable and possible to calculate, when we refer to managing risks, it is the quantitative measurements of knowable events. John von Neumann and Oskar Morgenstern in 1947 proved that expected value, which was derived

300 years ago, could be applied to utility function (**Figure 1.3.2c**). So for the events that happen with a probability, the expected utility can be calculated, so different choices with risks can be quantitatively compared for decision making. Such combination of utility theory and probability theory set the ground for decision theory (**Figure 1.3.2e**).

Utilities can also be experimentally measured in animals. Behaviorist B.F. Skinner studied animal behaviors with operant boxes, where test subject perform actions and receive reward or punishment. He argued that we should not be distracted to observe thoughts and feelings, but use environmental variables as incentives and reward to understand human behavior. Skinner's observation revealed that response frequency and speed of animal is a function of the effort of getting a reward, indicating the utility of given reward (**Figure 1.3.2d**). With the tools of expected utility for events with risk, we're ready to move into the wild full of different kinds of behaviors and solve decision-making problems. Before that, we also need to take several assumptions to make the formula work. Then we will be able to use powerful methods like payoff matrix, decision tree, etc. for assisting our decision-making process.

1.3.2 Rationality and decision analysis

The most important assumption that ensures expected utility theory to work is that all humans are rational. As René Descartes described concerning the rational human, we know what we want, and we are aware of the optimal way to obtain it. Besides being rational, the agent who is making a decision has to be consistent and self-interested, so the utility framework mentioned above can be fully functional. Gary Becker, who won the Nobel Prize in 1992 for his work on human behavior, developed the rational choice framework. This framework is widely applied to politics, crime, economics, and other realms. The rational and self-interested agent takes all information, including probability, cost, and benefits, and makes a determined choice. The preference is also assumed to be complete, which means the agent can decide which choice is preferable or if they are equally so. Moreover, the preference is transitive; for example, if the agent prefers apples to blueberries and prefers blueberries to cherries, then the agent prefers apples to cherries. (Becker 1978)

So as to analyze the decision and solve the problem, the primary task is to analyze the data and retrieve possible values for the problem. Then, given that relevant information and risks are known, the utility outcome can be evaluated. Under a simple decision environment, where decisions are binary, and results are binary as well, the outcome utility can be represented in a form of the matrix (**Figure 1.3.3**, North 1968). When a problem is more complex with more than one step, and there exists several alternatives or randomness in different steps, it can be represented by decision trees. In such a model, situations where

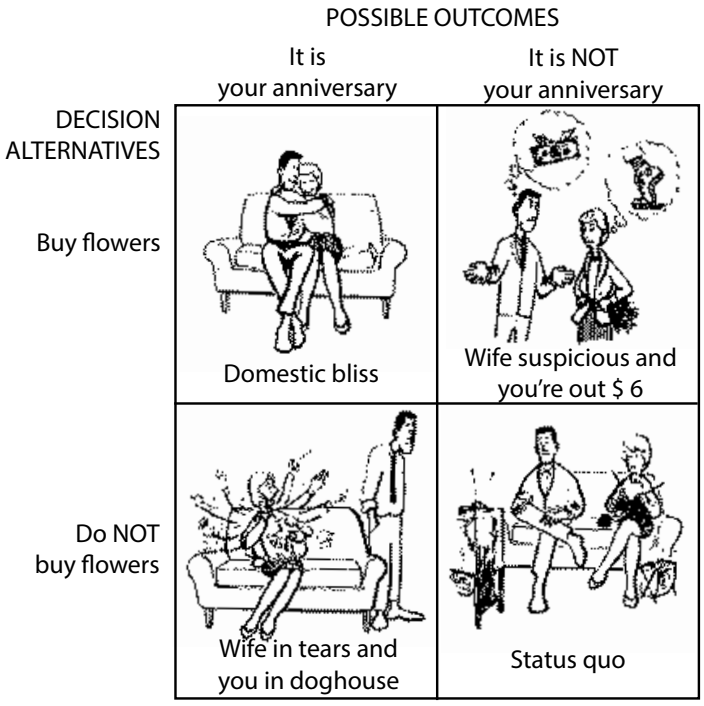

Figure 1.3.3: The payoff can be written as a matrix for the binary situation and the binary decision. In this particular example, the husband was driving home but suddenly recall it could be his wedding anniversary today. While the situation lies between it is the anniversary or not. And his decision could be either buy flowers or not. Thus the outcomes for all four combinations can be mapped onto the payoff matrix. (Modified from North 1968 with permission)

outcomes are partly random and partly under the control of a decision maker can be analyzed. One point of decision is a node, and different choice alternatives are coded as a fork at that decision point. The fork structure expands as the number of decision step increases for the problem to be solved, and it eventually unpacks as branches of a tree. (**Figure 1.3.4**, Raiffa 1968)

With the rationality assumptions, the decision-making agent can maximize the values and minimize the total cost given choice alternatives, payoff values at each alternative as well as constraints. To reach such goal, Herbert Simon proposed a three-stage sequential model for decision-making, consisting of intelligence, design and choice phase. In the first phase, the agent finds, identifies and formulates the problem or context that requires a decision to be made. In the design phase, all existing options, as well as newly developed alternatives will be researched under a pre-defined objective. The agent then evaluates all the options in the last phase and chooses one that gives the maximum value (Simon et al. 1987). Thus, even decisions involve complex trade-offs can be analyzed and optimized with existing mathematical frameworks embedded in such model.

Another key factor in decision-making is time. It came into economists' attention even before utility theory. Nineteenth-century economists already noticed that people does not only care about their immediate utility but also showed farsighted behaviors could potentially due to the expected future value.

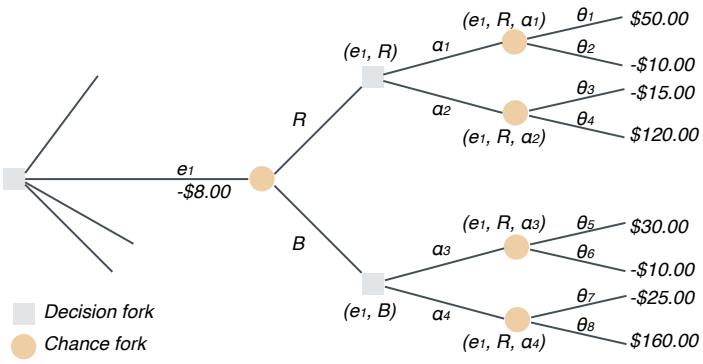

Figure 1.3.4: A sequential decision game represented by a decision tree. The player can choose $e1$ to start the game. Then a random colored (Red or Black) will determine which fork the player would proceed. The player can then choose freely from the available sets of alternatives among a. The outcome of either winning or losing money is determined by a random function θ after the player's decision.

Likely, future alternatives involve a risk of not getting or losing the value, and the temporal difference is inversely related to decision maker's value anticipation. In 1937, Paul Samuelson published a seminal paper and formulated the discounted utility model. Under the same rationality assumptions, discounted utility model describe one person's intertemporal utility function by multiplying the relative weights in a period of t. Taken together, the time dependency of utilities and probabilities adjustments allow for more accurate representation and evaluation of choice outcome.

1.3.3 Decisions in the real world

A widely used framework in many disciplines including economics, agriculture, robotics, queues for planning, decision-making, and reinforcement learning, is called the Markov decision process. In such process, one decision problem is represented by a set of states S, available actions A or risks are only dependent on the current state but not on decision history and reward R for given states and actions. The future reward is discounted by a factor γ taking a value between zero and one. Events such as a decision will trigger transitions from one state to another. As the Markov decision processed is defined, a policy π can be learned to illustrate a set of efficient action sequences. The optimal policy is found through value iteration or policy iteration.

There are many existing models different from Simon's choice model. Marvin Minsky proposed a model of human cognition that starts with backward-looking, analyzing past events, continuing with an abstract representation of the problem, and then using the model-predicted results or an experiment to determine a solution for a highly complex problem. Therefore, skills in mathematical techniques and knowledge of constraints and conditions are required. However, in practice, assumptions of rationality are rarely met, and an exceptional ability of mathematics is even harder to achieve. Therefore, many decisions are more often evaluated by smart heuristics for a fast and frugal process (Gigerenzer and Gaissmaier 2011). The trend

of tremendous growth of information challenges the classical frameworks, given the mountain of data that important decisions entail. Several decision support systems have been developed regarding the problem of data overload. For example, adaptive rules are widely used to improve the effectiveness of decision-making, such as tentativeness, delay, or hedging.

Another framework is called humble decision-making, which in contrast to rational decision-making, doesn't require full scanning of all available data and choice alternatives (Etzioni 1989). Humble decision-making is useful when one lacks knowledge of all alternatives, doesn't have a high amount of data, or is missing complete information but facing many alternatives. It provides two sets of policies in practice: the first one considers the global situation and gives a general direction, and the second involves incremental decisions to be implemented and particularized. A more extreme example is to rely only on simple heuristics, since it has shown a high effectiveness and a winning tendency, although such a process is only descriptive rather than prescriptive. When some people allocate their financial resources in investments, they rely on the 1/N rule (Thaler and Benartzi 2001). Comparing it to the other 14 advanced models, including the Nobel Prize-winning Markowitz's mean-variance portfolio, none can consistently beat the simple 1/N strategy concerning certainty equivalent returns, turnover and Sharpe ratio. These findings open a new chapter about how people can make (bad) decisions and at the same time be relatively successful on the planet.

"We think, each of us, that we're much more rational than we are. And we think that we make our decisions because we have good reasons to make them."

Daniel Kahneman

2

Psychology of Decisions

Richard Thaler was not the only noticed the failing of decision analysis theories in the real world. And the reasons are obvious because we are limited in our rationality. When we make decisions today, the environment we are situated in is like a jungle of complexity. So we can almost never have complete information or knowledge about our choices even when we are going to pick a jar of peanut butter. Our preference or belief are inconsistent over time or even within a few hours, and our ability of computation is severely limited even we are assisted by modern computers. To make decisions in such an environment full of frictions, many descriptive studies were performed, so that the real world techniques, tricks such as heuristics can be understood and applied within the scope of human cognition. More importantly, we know that mental shortcuts our brains are taking make approximations and simplify one problem, thus filling the gap between expected utility theory and reality. The studying of behavioral economics is a fascinating field of research which describes how our brains are making decisions, and scientists are even more surprised finding those results. As Daniel Kahneman delineated, there are thousand natural mistakes we can make in our decisions.

2.1 The thousand natural mistakes

When experts in finance thought they had superior knowledge, fine theories, and comprehensive information, in the subject, so they "know what they're doing", they had a hard time outperforming the simple 1/N simple strategy (Thaler and Benartzi 2001). Davis and colleagues went out to test if it is true in a controlled experiment setting. Three groups of people were given (1) basic information, (2) basic plus redundant information, or (3) basic plus non-redundant information. Both groups with extra information are significant more confident in making their choice, especially the group with non-redundant information feels the confident even significantly higher than the group with redundant information. However, both groups with extra information have their performance diminished miserably (Davis, Lohse, and Kottemann 1994). As Daniel J Boorstin phrased, *"The greatest obstacle to discovery is not ignorance, it is the illusion of knowledge."* From these findings we can already see information overload is maybe our enemy, but a bigger enemy is our obsession with information.

A higher level of confidence among other factors such as knowledge and skills give the decision-making agent a feeling of control. An experienced gambler might think he or she knows all the tricks of the game and has new faith in winning a game. Langer et al. did a comprehensive study in a game tested some hypothesis related to the topic of "illusion of control". They have shown that the test subjects cannot distinguish skills which determine outcomes from random chances. Giving them a choice increases their feeling as if they have control over outcomes, and the familiarity of the game further increases their confidence Langer 1975. Richard Feynman addressed his students in 1974 with following words, *"The first principle is that you must not fool yourself - and you are the easiest person to fool."* However, a worse news is that conscious deliberation makes an even worse outcome for decisions that involving consideration of many aspects, such as purchase a camera, buying a real estate (Dijksterhuis et al. 2006).

On the other hand, we don't perform conscious thinking frequently, which may save us from some disastrous choices, but it can be problematic too. When we rely on our intuitions and heuristic techniques too much, we easily became preys of Frederik's cognitive reflection test. He devised a series of "simple" questions, like "A ball and a bat cost $5.50. The ball costs $5.00 less than the bat. How much does the ball cost?" Frederick 2005. Many people would give a quick answer of $0.50, however, the right answer is the ball cost $0.25 and the bat cost $5.25. In the questions similar to this, the simple impulsive system is typically activated, so one would believe that the problem would be solved effortlessly. In many cases, it will succeed in a blink of an eye, but sometimes it requires much higher attention and activation of a controlled reflective system in the brain.

An interesting phenomenon is when we succeed in our decision, we attribute the positive outcomes

to our work, such as winning money from a portfolio in security investment. Whereas if we failed in our decision, we attribute adverse outcomes to external factors, as we blame a losing portfolio on a sudden crash of a big company or some natural disaster could never be foreseen, This phenomenon is formally known as self-serving bias. Of course one could never have predicted that to happen. We should feel no guilt of having such behavior, as no one expects a failure of his or her own action. It boosts our self-esteem but may not be optimal when we try to learn a lesson about what failed (Miller and Ross 1975). "Never ask a barber if you need a haircut", said Buffett, illustrating the tendencies that we seek a confirmation even if it is biased.

When we are trying to generate unbiased insights from the past events, it is also problematic because we tend to confirm our belief which might not even exist until we knew the outcome, known as the hindsight bias (Ariely 2010). "I knew it would happen all along". Like people claimed they predicted stock market would crash in 2008 way ahead of it happened, but those people never said anything before it took place. Moreover, we also render stories more compelling than facts. Legal cases were evaluated more convincing to the verdicts when items were constructed in the form of a narrative story. The orders of items presented also shift verdicts' evaluation, when they were presented in easy stories, they were rated more convincing, and the coherence of the story determines the strength of evidence of the items (Pennington and Hastie 1988, Gilovich, Griffin, and Kahneman 2002).

Many biases significantly affect our decisions, especially when we need to handle numeric problems such as personal finance. When one pick a portfolio in security investment, one tends to choose a disproportionate number of stocks or funds from home country because of "knowing" the companies. On the contrary, a rational agent should weight his or her choice based on many factors including percentage of GDP one country holds in the world. If Sweden's GDP is no more than 0.8% among all countries, it is, of cousre, wrong to build a portfolio with 70% values invested in the Swedish market (Cooper and Kaplanis 1994). Besides, when people examine the performance of their investment, they tend to have the status quo bias, which they use the buying value as a reference. As a result, one may end up with holding losing stocks even if those stocks were predicted to have ominous future because people are not comfortable selling them when it has not even reach status quo. Moreover, action bias is that we think at least do something is better than nothing, but it often worsens the investment choices. A trader who reacts to fluctuations in the stock market will lose more money compare to the ones set a long-term goal and stick to it. A football goalkeeper who always jumps to the side would perform worse even statistics showed he or she should sometimes stay in the middle.

Sunk cost bias would derail our decision process at one point we should only examine future outcomes. For example, we may need to compare option A with a profit of $1.00 million versus option B with a profit of $0.20 million in the near future with the same cost in the future. Some argument may rise like "But we have

spent $1.00 million in plan B already, it's almost finished" (Arkes and Blumer 1985). One related bias is called loss aversion, which describes the emotional utility gain associated with winning is way less than the emotional utility loss associated with losing. Avoiding "loss", even it is framed by a clever salesperson such as avoiding an extra charge in shipment rather than gaining a discount. Although one consumer may end up paying the same amount of money, avoiding "loss" will generate a higher level of pleasure (Kahneman 2013). The ownership of an item also biases our valuation. In an experiment, students were tested to trade mugs with money. The study has shown that when one owns a mug, he or she will only accept a much higher price to sell. But when one is ought to buy a mug, the person is willing to pay much less (Kahneman, Knetsch, and Thaler 1991). Therefore after some free trial period, one will feel the ownership of a product, like software, a TV, etc., and value the product much more, thus willing to pay for it.

Humans are also bad at evaluating outcomes with probability and time attached. We tend to overestimate the tiny probabilities such as winning a lottery, or the chance of one plane would crash, and underestimate a high probability as we may know there is a great chance stock market may crash. When the outcome is going to happen in the future, we are also inconsistent in our choices. When it was tested in children with two options, one was to to receive one marshmallow immediately, and the other was not to eat the one marshmallow and wait for a fixed amount of time to receive an extra marshmallow. Very few of them can resist the immediate temptation in order get the higher reward (Mischel, Ebbesen, and Zeiss 1972). Those biases can give troublesome consequences, for example, climate change does not give immediate impact on our lives or economy, and we discount the outcome that may happen in the future heavily. When we buy a mobile, TV, etc., we overestimate the chance that the item will break, and fall into the trap of buying extended warranty or insurances (Thaler and Sunstein 2009).

2.2 Beyond heuristics

2.2.1 Bounded rationality

All the biases when we make decisions come from a "satisfaction" after we make "good enough" decision, or "satisficing" as Herbert Simon combined "satisfy" and "suffice". The reason is that the limits of decision-making such as time, incomplete information, noise, cognitive capacity, attention span, and the inconsistency of our preference constrain our ability to make choices (Simon 1982). Instead, we use fast and frugal heuristics to achieve a swift and simple solution, sometimes those decisions even outperform complex mathematical models such as using the 1/N rule in stock market investment. A recent successful example is to predict weather 48 hours later in Sweden using an artificial neural network in a deep weather project.

Without knowing millions of parameters, aerodynamics, geophysics, or building sophisticated models with differential equations, an artificial neural network took all data into a giant black box, and reduced the prediction error mo more than 50% and operating time from three hours in traditional model to less than one minute.

Simon noticed that the alternative strategy contrasting to rational decision-making is the main strategy we are using to make decisions. He proposed a bounded rationality model in 1947 even before he proposed the framework for decision making (Simon 1997). The model suggested that humans are rational within a boundary, and it is the bounded rationality that tells us that we are not always able to find an optimal solution (Simon 1982). Instead, there are ways to structure and use existing resources to exploit what is at hand with clever heuristics to simplify our choices. We usually make choices use a combination of strategies, neither performing complex mathematical optimization nor being completely irrational. So we can be emotional, unsure about our preference, distracted, yet survive and succeed on the planet using the remaining parts of our rationality. Gilbert Keith Chesterton observed how rationality could be a pitfall in our decision-making a century ago, he phrased it as "Life is not an illogicality; yet it is a trap for logicians. It looks just a little more mathematical and regular than it is; its exactitude is obvious, but its inexactitude is hidden; its wildness lies in wait."

2.2.2 Prospect theory and choice architecture

Reinhard Selten and John Harsanyi worked on decisions with incomplete information, because of which they also awarded Nobel Prize. Such decision problems can be modeled with the introduction of a probability describing the uncertain state. It brings the decision-making model closer to bounded rationality. However, it is still challenging to capture the mechanisms behind all the biases. Also, Selten together with Gigerenzer developed a series of tools in real world applications, which take our cognition, emotions into the equation, solving the decision problem from the other side. One of the most successful achievements about the principles behind our cognition and decision making was the discovery of value function and probability weighting function from Amos Tversky and Daniel Kahneman, which later formed prospect theory (Kahneman and Tversky 1979, Tversky and Kahneman 1992).

The prospect theory expanded the expected utility theory to incorporate considerations of two biases discussed earlier. Instead of treating all the prospect probability and values equally, the prospect theory uses a reference point, where loss and gain are treated differently, the value decrease from a loss is approximately twice as much as utility gain. In addition, probabilities are weighted using real world measurement from subjectively perceived probability forming an S-shaped probability weighting function so that probability

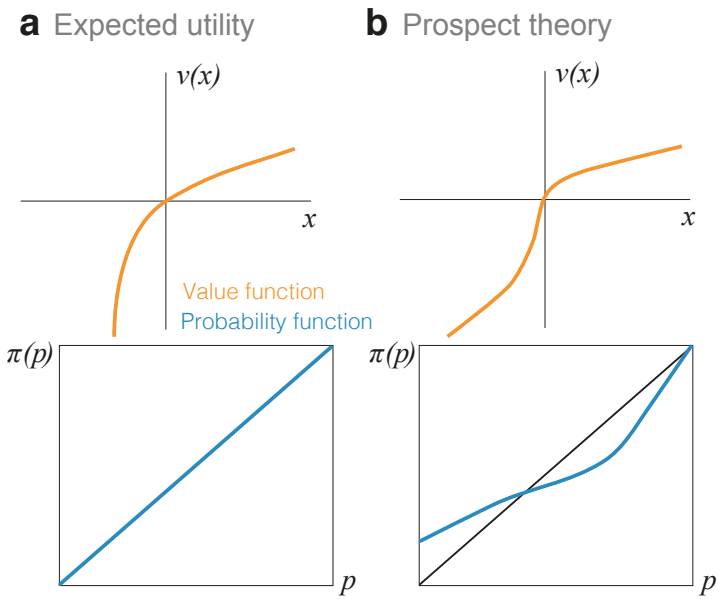

Figure 2.2.1: Decisions involve the valuation of rewards versus costs with a probability. **a** In expected utility theory, the prospect value equals the sum of the values of individual outcomes $v(x)$, and all probabilities are weighted the same $\pi(p)$. **b** In prospect theory, the value of the outcomes depending on a reference point, and weighted non-linearly by $\pi(p)$. (Modified from Rangel, Camerer, and Montague 2008 with permission)

bias is also accounted (**Figure 2.2.1**). This revised model also isolates other potential biases in our decision-making processes such as framing and status quo bias, explains some reasons behind why we aim after status quo in our investment strategy, or the reason why we fall into the traps of salesmanship. (Kahneman 2013)

Many studies focused on the application side developed our understanding further. Rober Schiller realized that not only individuals are bounded in rationality, the stock market is also limited in its rationality even if many brilliant minds are making decisions in every second. It is our emotions, again, collectively driving a big market. The automatic and impulsive system is the dominating system in many scenarios, which was described as early as 1935. Stroop used a simple task asked subjects to name the text color while the text semantic also contained information about color, however sometimes incongruent with its real color (Stroop 1935). How do we overrule the impulsive system in real life? Of course, after lengthy discussion, it should be evident that asking a decision-making agent to be rational is unlikely to realize. However, there are many tricks one can put into the design, to alleviate biases.

One of the most common design is the placement of switches on a kitchen stove. One can either linearly lay them on one line on the front panel, or place them with some jitter so each one match a cooktop. In the later design, which is more often the case in the modern kitchen stove, one doesn't need to pause and try to connect a switch and cooktop mentally every time before use (Norman and Berkrot 2011). Thaler and Sunstein described many different ways of design that can improve our decisions systematically, which they called choice architecture (Thaler and Sunstein 2009). Expected error takes our common error into account, and laid preventative measures against our impulsiveness. For example, an ATM would return

one's card first and later money because it expects the person to allocate his or her attention completely to getting the notes but forgetting to take back the plastic card.

Other designs cover different aspects in which we are prone to make errors. Choice structuring allows one agent to elimination by aspects by setting cutoff levels starting from the most important issue. For example, if one is buying a real estate, the budget may set the upper boundary, so one can say, filter out all the ones above 5 million SEK. The process iterate to the second most important aspect such as the distance of commuting to work (Tversky 1972). Besides, the mapping can converge all different value to a single measurement, so one doesn't need to convert monthly interest, quarterly administrative fees to a sensible unit, another example is converting the price of different items in the supermarket into SEK/kg or similar. Furthermore, feedback makes the adjustment of our decisions much faster, such as the viewing hood of a digital camera, so a process of adaptation can speed up to seconds. A parking radar makes the parking much easier and faster.

Nudging the emotions, either pleasant or unpleasant one also significantly change people's behavior and satisfaction afterward. When I was in University in China, public shower was the only place one can wash oneself with warm water. Instead of paying for the amount of water beforehand or afterward, the system was designed that one put the plastic card in a tiny machine, and this machine updated how much you pay with every 10 cents increase. It was extremely painful to take a warm shower while having all the attention to coins draining out of one's pocket, but it was designed to make people save more water and money. Conversely, Thaler and Benartzi created a less painful system that one should only commit to saving with his or her future self. Instead of asking people to save more now, they recommended people to put their next salary raise into a saving account, which we of course, discount its utility because it will happen in the far future (Thaler and Sunstein 2009).

"There is no scientific study more vital to man than the study of his own brain. Our entire view of the universe depends on it."

Francis Crick

3

Neuroscience of Decisions

Following the work and discussion about the analysis of decisions, the psychology of decisions, we know the mathematics, our errors, and how to prevent biases in decision-making. Simon et al. wrote an article describing that the function of human society and daily jobs from all disciplines are primarily composed of decision-making and problem-solving. Among the authors, many of them are renowned economists, scientists or Nobel laureates including Dantzig, Schelling, Thaler, and Tversky (Simon et al. 1987). Although it is imperative for our lives and society, a key piece of the puzzle is still missing. The brain exclusively performs our decisions, and luckily we have acquired an enormous amount of information about this organ regarding its structure and functions. Both human and animals can easily associate their actions to outcomes, and use such association as evidence for future references. The brain can also easily represent outcomes as positive, negative or neutral reinforcers (Skinner 1938) even with complications such as delays or uncertainty (Cardinal 2006).

With modern technologies in neuroscience, we learned that the brain is regionally specialized for different tasks. For example, the motor cortex is responsible for our locomotion, the visual cortex is for visual sensory information processing, and the hippocampus (HPC) is for memory encoding. It comes as no

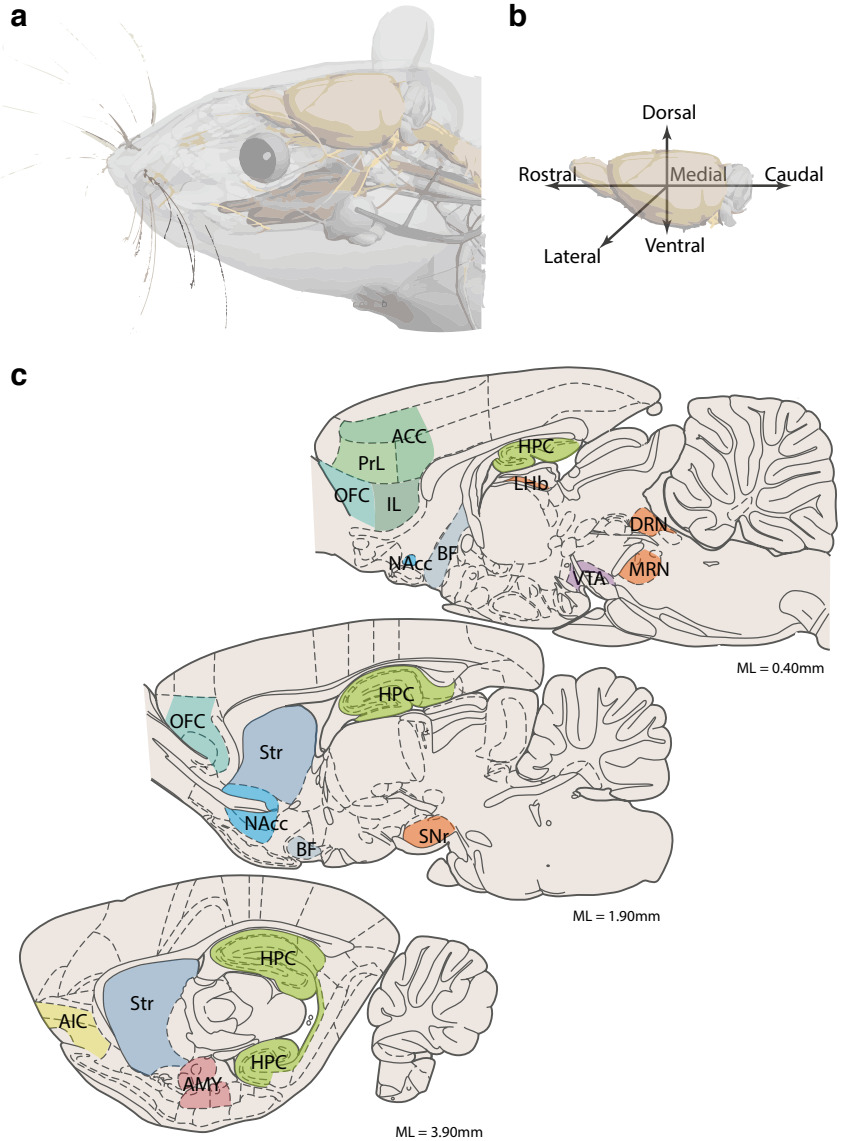

Figure 3.0.1: **a** Illustration of the location of the rat brain. **b** Standard anatomical reference of the rat brain anatomy. **c** Regions are commonly referred to in this thesis are labelled in color in a series of sagittal sections along the medial-lateral axis. PFC, prefrontal cortex; PrL, prelimbic cortex; ACC, anterior cingulate cortex; IL, infralimbic cortex; BF, basal forebrain; NAcc, nucleus accumbens; HPC, hippocampus; LHb, lateral habenula; DRN, dorsal raphe nucleus; MRN, median raphe nucleus; VTA, ventral tegmental area; Str, striatum; SNr, substantia nigra pars compacta; AIC, anterior insular cortex; AMYG, amygdala.

surprise that the brain has ways of assessing information and making decisions. Tversky and Kahneman proposed there are broadly two systems in our brains for decision-making. The proposal is conceptually useful for two broad situations involving the point that either fast actions or careful considerations are required from the behaviorists' and economists' perspectives (Kahneman 2013). On the one hand, information that is intuitive allows humans and other animals to make fast and cheap moves that are essential for living functions such as survival. These situations lead to immediate consequences, but they do not necessarily lead to bad decisions. On the other hand, logical or numerical problems, which typically involve non-certain outcomes or delayed results, require decisions made with much deliberation; however, they are not guaranteed to give pleasing results.

Several specialized brain regions were identified to have equivalent functions to the two-system notion in decision-making. For example, the amygdala (AMYG) signals danger, pain, and efforts in a short prospect, whereas the medial prefrontal (PFC) area signals the prospect of the future (Bechara 2005). These regions can be approximately classified into two groups; the first group (impulsive system) are involved in procedure actions in response to a stimulus, while the second group (reflective system) are involved in goal-directed behaviors. The reflective system is far more complex than the impulsive system, and it triggers the activation of a series of brain regions including the ones also used in the impulsive system. As a decision-making agent, one must retrieve the action-outcome information encoded earlier, and compare representations to other alternatives in the brain. For this purpose, memory is also recalled to generate affective reactions and prospects. Affective states, in addition to the memory system, is also regulated by the hedonic brain stem parabrachial nuclei and the midbrain raphe nucleus. While an affective state is represented in the AMYG or in the PFC, it is more specifically represented in the anterior insular cortex (AIC), and somatosensory cortices. The reflective process is procedurally resolved through the work of many more brain regions. The process involves the orbitofrontal cortex (OFC), dorsal lateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), HPC, nucleus accumbens (NAcc) (**Figure 3.0.1**), with collective computation of memory, attention, impulsive control and valuation.

The whole decision-making process in the context of neuroscience will be discussed in more detail in the coming sections, begins with the foremost mechanism, top-down control of attention. Top-down control directed by the PFC determines the outcome of a decision. First of all, with scarce brain resources, attention is allocated to one particular problem, and then the reflective system can start functioning to resolve the problem and later also reflect on the consequences of its choice. However, it is unlikely that only one mechanism is involved in such a complicated process. Conceptually, divergent functions such as cognitive flexibility, automatic response restraints, the resistance of distracting information and many other mechanisms can converge and generate the same behavioral outcome. Some of these mechanisms within the

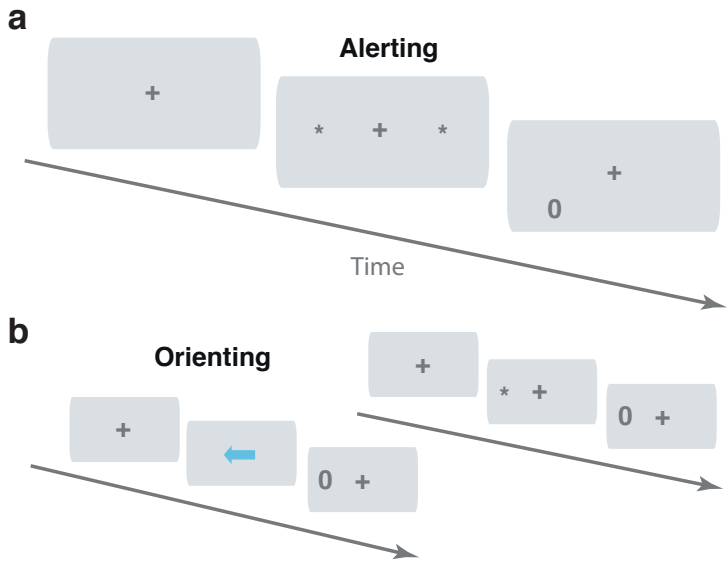

Figure 3.1.1: Types of attention includes: **a** In alerting task, a cue will be presented to the subject that a target is about to appear, however no information about target location. **b** In orienting task, subject is required to fixate its eyes on the center, then it is required to pay attention to specific location with help of the cue. (Modified from Raz and Buhle 2006 with permission)

scope of the thesis study will be discussed in greater detail.

3.1 Attention

The mechanism behind attention has been long debated, with many parallel hypotheses existing from the modulation of sensory gain threshold (Singer, Zihl, and Pöppel 1977), dynamic information processing via synchrony (Engel, Fries, and Singer 2001), and filtering of irrelevant information (Broadbent 1987, Fries 2009). However, none of these hypotheses can fully explain the process. Researchers are aware of the limitations in methodology, which constrain our full understanding of the mechanisms of attention. Nevertheless, it can be agreed upon that brain regions such as the PFC and frontal eye fields play critical roles in attentional informational processing. Furthermore, there is also a consensus that attention is crucial for our daily tasks such as self-control or emotion control (Posner and Rothbart 1998), especially during the development of young children (Posner and Rothbart 2000).

3.1.1 Topology of attention

In 1890, psychologist William James described attention as the taking that clears one object or thought out of several simultaneous or series ones. Attention is one of the pivotal issues in decision making as it delineates the preparedness and selection of specific stimuli in the external environment, individual goals represented or memories stored internally in the brain. Besides, the function of top-down attention illustrates

one mechanism of how the reflective system is exerted over the impulsive system. Posner and colleagues studied patients with focal brain injuries and associated deficits in their attention-related behaviors. Then they formed the insights that attention is controlled by independent networks within the brain, and they proposed three major functions of attention (Posner and Boies 1971, Posner and Petersen 1990).

The main functions of attention enable (1) orienting to sensory stimuli, (2) detection of the salient signal for deliberate cognitive process, and (3) sustaining an alert or vigilant status (Raz and Buhle 2006, **Figure 3.1.1**). More specifically, orienting allows selection of specific information among distinct locations, responds more rapidly, and guides eye movement to the target location. Detection allows supervisory or selective attention, so test subjects can report a target event or an error, plan an action, overrule the impulsive system, or resolve conflicts. Alert allows preparation for processing valuable information, maintains vigilance for an imminent stimulus, and sustains the response to receiving the maximum payoff.

There are parallel models that cluster mechanisms of attention differently, although they are similar in describing behavioral outcomes. Kastner and Ungerleider proposed that top-down attention is controlled by the cortical-biased competition, which includes (1) enhancing neuronal response to stimuli, (2) counteracting suppression between distractors and stimuli, (3) altering baseline neuronal activities, and (4) enhancing neuronal sensitivity to stimuli (Kastner and Ungerleider 2000). Given the importance of attention as a prerequisite for decision-making, it shapes our general daily behaviors. However, it is challenging to unify all the theories and experimental findings. Using animal models allows precise manipulation of subpopulations of neurons or specific circuits in the brain although there is still a gap, in which top-down attention is typically studied in human or primates, whereas the current molecular toolbox is largely restricted to mice or primitive species.

3.1.2 Decisions with attention guide

Attention demands an abundance of cognitive power, and humans or animals tend to save such scarce resource for the situation when it is really required. The process of decision-making is a typical example, in which attention is allocated toward the unknown for collecting relevant information about the problem to be solved. Moreover, attention is also needed in caring for external environmental in general, such as in a foraging behavior. Primarily, attention is allocated to high values options, low-cost alternatives for motivation, planning, execution and evaluation of goal-directed behavior. Before we begin the discussion about lab research of attention, we should realize that those experimental settings are highly constrained with many variables fixed for control (Manohar and Husain 2013, Gottlieb et al. 2014). In real life scenarios, however, especially in the information age today, there is a high demand for our attention to be sustained

for the accumulation of new evidence for adjusting our actions and plans according to new coming information or stimuli. However, it is questionable if we have longer lasting attention compared to a hundred years ago.

We noticed that people often have unsuccessful attempts to act in their best interest. We make bad investments in the stock market, bad savings for the retirement plan, and bad career choices all the time. Suri and colleagues manipulated orienting attention in human subjects without changing the value of the choices, and they found increased motivation levels and valuation of the high attended choicec (Suri and Gross 2015). Conversely, higher reward value can enhance the level of sustained attention in the subjects, who is also willing to pay a higher cost (Massar et al. 2016). Deficits in attention, on the other hand, are often accompanied by impairment in decision-making. Adults with attention deficit hyperactive disorder (ADHD) have shown impaired functions in reinforcement learning as well as an increased preference towards risky options (Mowinckel et al. 2015). Patients with depressive-like symptoms also exhibit similar deficits, but their performance can be improved after attention training sessions (Cooper et al. 2014).

The PFC and parietal regions have been repeatedly linked to attention from studies with neuroimaging, and electrophysiology in patients, healthy volunteers, or animals (Li et al. 2010, Miller and Buschman 2013), and top-down attention is associated with increased neuronal activities in the PFC (Buschman and Miller 2007). Children with ADHD have been shown with impairment of reward processing in the ACC (Umemoto et al. 2014), while children with damage to the mPFC exhibit deficits in the processing of attention and altered regulation of emotion (Sánchez-Navarro et al. 2014). Neuroimaging results have revealed that patients with ADHD have shorter-lasting activation of the dlPFC, vPFC, and AIC and fail to activate the ACC and HPC afterward (Ernst et al. 2003). Some functional regions were confirmed after causal manipulation of the brain activity. The angular gyrus in the parietal cortex is sensitive to attention and risk. Inactivation of the region using rTMS specifically altered the decision latencies as well as outcomes in the trials where visual attention was required but not in the trials requiring auditory attention (Studer, Cen, and Walsh 2014).

An animal model with PFC lesions has illustrated that neuronal response modulated by attention is reduced in the visual areas (Gregoriou et al. 2014). Lesions in the ACC of rats impair visual attention needed for discrimination of task-related stimuli, thus decreasing choice accuracy (Kim et al. 2016b). Activation of the PFC facilitates gating of sensory information (Moore and Armstrong 2003), more specifically, descending projections from the PFC differentially regulates neuronal activities in the visual cortex, enhancing neuronal response and sensitivity for discrimination (Zhang et al. 2014). Activation of the descending PFC projections is also linked to specific regulation of cortical-basal ganglia interaction during attention processing (Schouwenburg, Ouden, and Cools 2015). Moreover, additional areas are also involved in at-

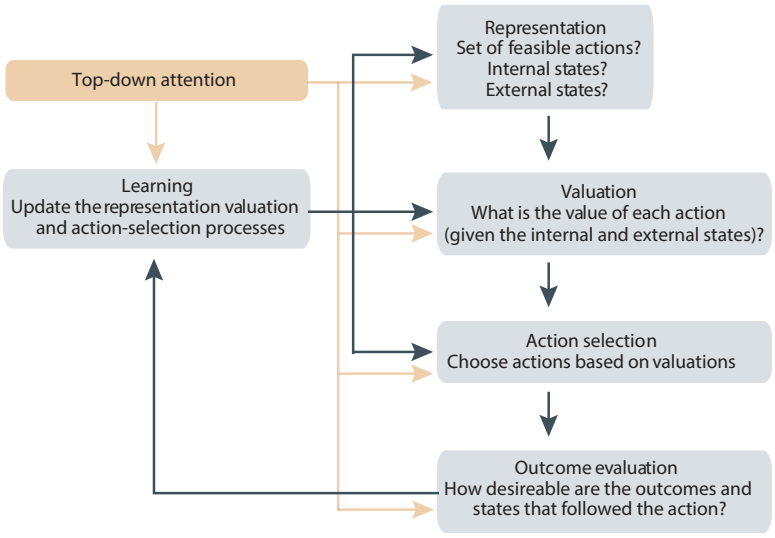

Figure 3.2.1: Value-based decision making is consist of five fundamental steps. The decision problem is constructed for a brain representation, then actions and outcomes are evaluated. Third, one action can be selected based on the valuation. After implementation of the decision, the outcome is evaluated. Finally the information for the outcome is used to update the previous processes. (Modified from Rangel, Camerer, and Montague 2008 with permission)

tention processing such as the superior colliculus, pulvinar, and temporoparietal junction (Baluch and Itti 2011).

3.2 Decision framework

Moving forward from the top-down system of guided attention, which is the prerequisite of any decision-making problem, the brain provides resources and focuses on the events or problem for which we are trying to gather information or solve. Those events or problems range from simple foraging behavior in primitive species to complex portfolio optimization in stock market trading. The decision alternatives also range from one alternative to a combination of hundreds of choices. To understand the decision-making process in the context of neuroscience, we are going to examine the process in several discrete steps. It includes generating the desire and need, collecting information for the problem, analysis of the alternatives, committing to some strategy, and assessment of the outcome (Rangel, Camerer, and Montague 2008, Doya 2008, **Figure 3.2.1**). External factors such as uncertainty, time left or time spent is known to bias the process psychologically, as it was discussed in the previously chapter. Internal neuronal computations, as the focus in this part, is the key to a unified understanding of discrete steps in decision making.

3.2.1 Neuronal computation for decision making

Representation

To carry out the neuronal computation for decision-making, the entire problem needs to be represented in the brain. Unfortunately, we still have no knowledge how it is done. This leaves open questions like it the decision problem represented as a master function? Does it take variables such as internal drive or memory? Where in the brain is this master function operated? How could relevant information be correctly retrieved, and noise to rejected? Sadly, not knowing how the problem is represented leave us to explore in the dark, it's as we can do as much as deep sequencing of the genome, but we still have to guess without knowing DNA coding system. Regardless of the limitations, we know representation in the brain is conceptually important for referring to an internal drive status such as desire or need. Besides, it also integrates information from the external environment such as weather or space, and then it mentally sets up potential alternatives on which to act (Gallistel 1989, **Figure 3.2.2b**).

This is useful in that we can break down the problem into smaller pieces. Although we don't know how the decision problem is represented as a whole, investigating how values, costs, or actions are represented in the brain is possible. Moreover, it is even more useful when we make a hypothesis and conduct an experiment. Midbrain dopaminergic neurons have been known to encode a reward, and their firing patterns can even predict a reward (Schultz, Dayan, and Montague 1997). The ventral tegmental area (VTA) receives inputs from a large number of areas ranging from the forebrain to the brain stem. Descending projections from the PFC regulate reward and aversion in mice (Lammel et al. 2012); glutamatergic projections from the dorsal raphe nucleus (DRN) also signal reward (Liu et al. 2014), and projections from the lateral habenula (LHb) send negative reward signals to the VTA (Matsumoto and Hikosaka 2007). Another known system of representation is a spatial map in the entorhinal cortex. Such representation provides an internal map of the external environment (Moser, Kropff, and Moser 2008), and the AMYG is found to be one hub integrating information of space and value (Peck, Lau, and Salzman 2013).

Valuation After the decision-making problem is represented in the brain, utilities are assigned to different alternatives for proper comparison, planning, an optimal strategy, and action. The utilities, however, can be difficult to obtain sometimes as we cannot always know outcomes immediately with high certainty. Computation, in which utilities are assigned to a particular part of the brain, is performed taking account of variables like a reward, cost, and desire. The PFC is one of the key regions in the utility computation. *In vivo* recording in behaving primates has shown the dlPFC, and OFC adaptively encodes goal utilities, optimizing the animal's behavior over time (Barraclough, Conroy, and Lee 2004). Functional neuroimaging also reveals that the vmPFC calculates expected utilities, and reward outcomes and monitors hedonic gains

during the decision (Grabenhorst and Rolls 2011).

The OFC attracts a fair amount of attention in research about valuation. Neurons in the OFC encode value (Padoa-Schioppa and Assad 2006) and interact with the basolateral AMYG, mPFC (Cardinal et al. 2002), and ventral and the dorsomedial Str (Yin, Knowlton, and Balleine 2005) in processing valuation and expected outcome relationships. In behaving rats, the OFC and mPFC encode animals' previous action and outcomes over time, and the OFC further encodes the value of choice and predicted error whereas the ACC is activated shortly before the action of test subjects (Sul et al. 2010). It was later illustrated further that the OFC neurons evaluate current and previous choices, whereas the ACC neurons encode choice itself and the prediction error (Kennerley, Behrens, and Wallis 2011). The neuronal coding is also showed in primates, where value coding the OFC neuronal activities can also dynamically adapt to change in reward distribution over time (Kobayashi, Carvalho, and Schultz 2010). Lesion of the OFC neurons in rats significantly changes error coding of DA neurons in the VTA specifically linked to the integration of internal information (Takahashi et al. 2011). Interestingly, neurons in the VTA exhibit specialized functions, where GABAergic neurons encode expected reward, and dopaminergic neurons encode prediction error and actual outcome (Cohen et al. 2012), drive reinforcement (Steinberg et al. 2013).

Another side of the coin is cost. Loss or aversive events were linked to the AMYG and LHb (Yacubian et al. 2006), such events can increase the level of arousal and attention. Neurophysiological data has revealed that neurons in the AMYG encode both expected and unexpected reward and punishment differentially (Belova et al. 2007). In addition, the posterior Str (Seymour et al. 2007, Preuschoff, Bossaerts, and Quartz 2006), inferior parietal cortex (Tom et al. 2007), and AIC (Dreher, Kohn, and Berman 2006) are also linked to respond to loss. Patients with the vmPFC damage exhibit a significantly high probability of risk-seeking behavior (Bechara 2003). Neuroimaging studies further show that the NAcc is associated with risk-seeking behavior, and the AIC is associated with risk-aversion behavior (Kuhnen and Knutson 2005). The uncertainty of the outcome is also encoded in the same set of cortical areas, including the AIC (Huettel et al. 2006) and the OFC (Hsu et al. 2005).

Delay also plays a critical role in the valuation process (**Figure 3.2.2c**). We realized more than a century ago that future utilities are discounted, and there exists several models for the phenomenon (Samuelson 1937, Ainslie 1975). Human neuroimaging studies have shown that distinct neural systems involve in processing immediate utilities versus temporally delayed ones. The lateral PFC and the Str have been shown activated for the smaller sooner (SS) reward, whereas the dlPFC, DRN, and inferior parietal cortex are activated for the delayed outcomes (Tanaka et al. 2004, McClure et al. 2004). The valuation can be further grouped into positive evaluation in the vmPFC and inverse evaluation in the ACC and AIC (Prévost et al. 2010). Inactivation of the human dlPFC using rTSM confirmed their roles in waiting for delayed reward

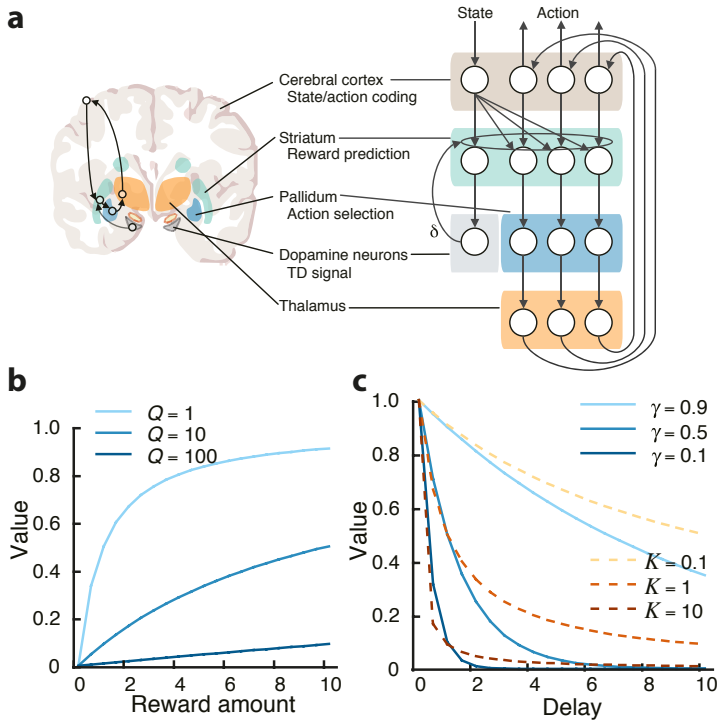

Figure 3.2.2: **a** Topographical organizations of major anatomical regions involving decision making (Left: coronal section of the human brain; Right: functional diagram). **b** Saturation of the utility function, where Q determines saturation. c. Temporal discounting function for delay d, where γ is the discount factor for exponential discounting, and K determines steepness of hyperbolic discounting. (Modified from Doya 2008 with permission)

(Figner et al. 2010). Neurons in the OFC have been later shown to have a more specific role in confidence judgment of time (Lak et al. 2014), and neurons in the ventral Str encode the expected sum of temporally discounted values (Cai, Kim, and Lee 2011).

Action When the action is needed to be performed, different values are compared for the decision agent to make an optimal action. Again, how the computation is done for the goal-directed behavior is largely unknown. It leaves many open questions. What is compared to make a choice? Is the difference between utilities or the absolute utilities compared? Are different utilities represented in the same computation unit? How can the result be coded and relayed to the action machinery? There are several hypotheses in the research field of perceptual decision making, one of them being the top-down control system allocates control through competitive racing toward one threshold (Heekeren, Marrett, and Ungerleider 2008).

Recording in the primate PFC has revealed that there exists a high level of the motor planning signal, which can further predict their locomotion before any action takes place (Kim and Shadlen 1999). Human imaging studies have revealed the dlPFC exhibits a capacity of executive control, and performance monitoring (Critchley et al. 2003), and the ACC responds to conflicts and encodes performance adjustment (Ridderinkhof et al. 2004). Such adjustment was impaired in subjects with ACC damage (Shenhav,

Botvinick, and Cohen 2013). The neuronal activities in the ACC also encode the cognitive load of the task, predicting the difficulties of the task, which important for the continuous adaptation of action for optimal outcomes (Sheth et al. 2012).

Reevaluation and belief update The brain is then required to measure the benefits from the outcome after the action is performed. This new information will be used in return to update the original belief of the expected outcome and stored for future usage in a similar situation. Significant activation of the human OFC responds to outcome receipt with outcomes (Zink et al. 2004), but negatively correlates to the degree of hedonic feelings in humans (Kringelbach et al. 2003) or the amount of value one expects (Rudebeck and Murray 2014). Therefore, the OFC is believed in the assessment of value; internal states for optimal decisions and lesions in the animals OFC induce high preference of SS choice (Mobini et al. 2002). On the contrary, damage in the mPFC does not produce any bias between SS reward and LL reward (Cardinal et al. 2001).

Lesions in the mPFC, instead, impair usage of learned information from the outcome in the future behavior (Coutureau and Killcross 2003). Moreover, GABAergic neurons in the mPFC have been recently shown to project to the NAcc, and optogenetic stimulation can produce an acute avoidance behavior (Lee et al. 2014). Other regions such as the ACC and AIC are also linked to outcome evaluation in humans (Breiter et al. 2001) or in primates (Seo and Lee 2007). The ACC has been shown to encode both the absolute value and the sign of prediction error associated with behavioral outcomes (Ide et al. 2013). Midbrain dopaminergic neurons are believed to be the source of prediction-error and belief updates. The existence has been reliably demonstrated via electrophysiological recordings in the VTA of the brains of behaving monkeys (Schultz 2016, Schultz, Dayan, and Montague 1997). The AMYG and ventral Str also make distinct contributions in both outcome evaluation and information update; the AMYG decreases learning rate and action consistency, but the ventral Str modulates speed-accuracy trade-off (Costa et al. 2016).

After the reevaluation of all the previous information has been updated, regions such as the OFC are known to integrate internal drives, external stimuli, and the goal. It encodes the level of desirability of the outcome; therefore, it facilitates learning (Schoenbaum and Roesch 2005). Thus, there are open questions that address the computational details of the process of updating. Where and how is the outcome represented? Is it represented in the same computational unit as the original belief? Is the error or the absolute value of the expected outcome stored or updated? Is the original belief is updated with some inference based on historical outcomes or does new outcome overwrite recent belief?

3.2.2 Modulators of neuronal computation

Besides factors like internal desires, uncertainty and risks, and time, there are several known mechanisms of neural modulation involved in the process of decision-making (Doya 2008, **Figure 3.2.2a**). In the domain of time and effort, recording in the VTA and DRN has shown distinct encoding for the two populations: the VTA neurons encode both effort and delay, while, the DRN neurons only encode delay (Denk et al. 2005). Moreover, manipulation of the serotonergic system can alter the effort one is willing to exert (Meyniel et al. 2016), and change animals' tolerance to delay (Miyazaki et al. 2014, Fonseca, Murakami, and Mainen 2015). More recently, the ascending 5-HT neurons from the DRN to OFC are shown encoding expected outcomes (Zhou et al. 2015).

As discussed earlier, the AMYG and LHb are involved in cost or loss, and a group of GABAergic neurons projecting from the VTA to LHb suppresses the activity of the LHb, which in turn project back to the VTA, increase the firing of dopaminergic neurons, and promote reward (Stamatakis et al. 2013). In the animals with lesions in the OFC, dopaminergic neurons failed to integrate internal drive status, thus altering their error signaling and future value encoding (Takahashi et al. 2011). To mimic the effect of DA in the Str, dopamine receptors 1 and 2 can be easily targeted. Inhibition of D2-expressing neurons can increase the probability of choosing higher valued alternative (Jocham, Klein, and Ullsperger 2011). Using optogenetic stimulation of either D1- or D2-expressing neurons produced opposing outcomes of their decisions, reflecting a change in their action value (Tai et al. 2012).

"I regard the brain as a computer which will stop working when its components fail."

Stephen Hawking

4

Biological Building Blocks

It is impossible to understand how our brains make decisions without a deep appreciation of the brain's components: neurons. The areas of the brain are interconnected by hundreds of billions of neurons and quadrillions of synapses (Kandel et al. 2012). Recent advances in technology have made many questions that were previously impossible to address reachable. The genetic profiling of nerve cells enables the fingerprinting of specific subgroups of neurons, and the later creation of tools makes selective targeting of a sub-population of choice possible (Huang and Zeng 2013). A new retrograde tracing method allows us to dissect monosynaptic connections between distinct neuron populations among brain regions (Wickersham et al. 2007). Novel neurochemistry methods such as CLARITY make it possible to visualize neurons in one whole brain (Chung and Deisseroth 2013), and a new imaging method called light-sheet microscopy tremendously accelerate the image acquisition (Tomer et al. 2015). Furthermore, *in vivo* optical imaging opens the door to understanding the circuitry behaviors of hundreds of neurons simultaneously and in real time (Chen et al. 2013).

4.1 Local circuitry

Neurons in the vertebrate cortex are organized in columns, which are often associated with specific functions; for example, the barrel cortex controls whisker movement in rodents (Petersen 2007). The structural organization and electrophysiological and behavioral output are often studied at the level of microcircuitry within the limit of current technological feasibility, focusing on detailed scrutinizing of a compact brain region. Neurons in the networks can be broadly classified into two classes: principal neurons and interneurons. Principal neurons release glutamate as the neurotransmitter, inducing excitatory responses in post-synaptic neurons. They are the basic arithmetic components that carry out computations and information processing in the cortex. They have a triangle-shaped cell body and are, therefore, also referred to as pyramidal neurons. The principal neurons constitute more than 80% of the neuronal population in the human cerebral cortex. The interneurons are much smaller in number but are highly diverse in terms of morphology, connectivity, and physiology (**Figure 4.1.1a**, Tremblay, Lee, and Rudy 2016). Interneurons project locally and release GABA as a neurotransmitter, inducing inhibitory responses in post-synaptic neurons. They provide feedback inhibition, information relay, information gating and other regulatory mechanisms in the microcircuitry.

4.1.1 Cortical interneurons

As mentioned, the interneurons represent a minority of the cortical neurons, and this population has been extensively studied in past decades.Interneurons add dynamics to cortical computation and, thus, carry out functions that are critical to behavior. Using extracellular recordings *in vivo*, one can examine their temporal dynamics and engagement in a particular neural population under different behavioral contingencies, which are currently most well understood in the hippocampus (Klausberger et al. 2003). Traditionally, cortical interneurons were believed to coordinate recurrent excitations in local networks and safeguard rhythmic neuronal activities, filtering out runaway excitations (Douglas et al. 1995). More recently, using Cre driver lines, interneurons have been shown to modulate the information flow in local circuits and alter the functional output of the network (Kepecs and Fishell 2014). There are additional functions that cortical interneurons carry out, including providing feed-forward information to the principal neurons (Mallet et al. 2005), and increasing the temporal fidelity of principal neurons (Pouille and Scanziani 2001). It should be noted that transgenic Cre driver lines only provide approximations of the larger subtypes of interneurons and do not capture homogeneous interneuron populations with high fidelity nor do they precisely represent the cardinal interneuron types identified (Xu, Roby, and Callaway 2010, Rudy et al. 2011).

More importantly, we started to put the puzzle of cortical computations together by narrowing down

specific functional neuronal output organizations, specific interneuron types, and their temporal firing patterns. With genetic tools, it has been shown that interneurons in the mouse visual cortex are organized in a highly specific pattern, with parvalbumin (PV) interneurons strongly inhibiting other PV interneurons, but weakly inhibiting other types of interneurons. Somatostatin (SST) interneurons inhibit PV and vasointestinal peptide (VIP) interneurons and VIP interneurons preferentially target SST cells (Pfeffer et al. 2013). In freely behaving animals, the different types of interneurons respond differently to behavioral events, with distinct temporal dynamics in each subgroup (Kepecs and Fishell 2014, **Figure 4.1.1b**). Interneurons also provide gain control of principle neurons, thereby changing the input-output function by synchronization, shunting or non-linear decomposition (Mitchell and Silver 2003, Schwartz and Simoncelli 2001, Renart et al. 2010). Computer-like arithmetic such as subtraction and division can be achieved through inhibition (Silver 2010, Carandini and Heeger 2011). Moreover, inhibitory interneurons also play a role in controlling the timing of spikes in a particular neural population (Vreeswijk and Sompolinsky 1996), enhance sensitivity by sharpening tuning in the auditory cortex (Wehr and Zador 2003), change the temporal-spatial response of neurons for visual information processing (Haider, Häusser, and Carandini 2013), and normalize the activities of local excitatory pyramidal neurons (Carandini and Heeger 2011).

4.1.2 Fast-spiking interneurons

Fast-spiking parvalbumin (FS-PV) neurons are an important subgroup of interneurons that enrich the repertoire of neural dynamics and are believed to keep a fine balance between excitation and inhibition (Hu, Gan, and Jonas 2014). The hallmark of FS-PV neurons is their ability for fast signaling action potential to downstream neurons as a result of their specialized adapted synaptic output structure (Hu and Jonas 2014) and nanodomain coupled to calcium channels for efficient GABA release (Bucurenciu et al. 2008). There are two notable major subtypes of parvalbumin interneurons, distinguished by their morphology and synaptic connection patterns. FS-PV basket cells target the soma of principal neurons, and FS-PV chandelier neurons target the axon hillock effectively and regulate the spike generation of principal neurons. In the hippocampus, PV neurons represent only 2.6% of the total population (Bezaire and Soltesz 2013). However, their functions are not only restricted to simply inhibiting the network. Instead, they control spike timing, firing rate, and burst activities of place cells by inhibiting dendrites and soma (Royer et al. 2012). A remarkable configuration of the FS-PV network is the reciprocal coupling between FS-PV neurons and pyramidal neurons, which provide the infrastructure for feedforward and feedback inhibition on principal cells. In the feedforward circuit, FS-PV cells generate robust inhibitory conductance, monitoring the time window for incoming excitatory spikes, and increasing the dynamic range for action potential integration

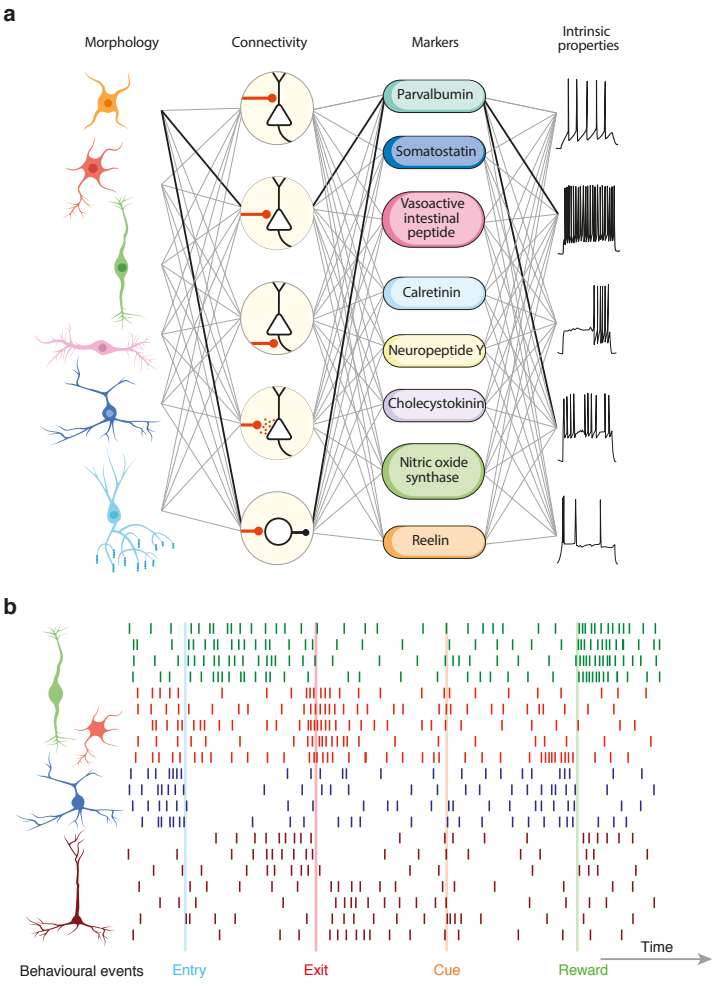

Figure 4.1.1: **a** Interneurons in the CNS can be classified based on measurements including morphology, connectivity, molecular marker expression profiles or intrinsic electrophysiological properties. **b** Neurons respond to different behavioral events showing as raster plot in a time course. (Green: VIP, Red: PV, Blue: SST; Brown: pyramidal neuron) (Modified from Kepecs and Fishell 2014 with permission)

(Pouille and Scanziani 2001). On the contrary, the feedback circuit contributes to recurrent and lateral inhibition, forming the basic information processing network such as the space grid (Couey et al. 2013).

FS-PV neurons are highly coupled among themselves, connected by electrical synapses and GABAergic synapse. This organization of connected FS-PV neurons enables synchronous spiking activities and coordinates cortical oscillations (Galarreta and Hestrin 1999, Buzsáki and Wang 2012). FS-PV neuronal activities are dynamically adapted to ongoing behaviors and associated with events such as memory consolidation in the hippocampus (Lapray et al. 2012). Conversely, the optogenetic driving of FS-PV neurons in the mouse somatosensory cortex has been shown to increase oscillations in the gamma range and gate sensory response of excitatory neurons (Cardin et al. 2009, Sohal et al. 2009). An increase in oscillatory gamma activity can enhance sensory detection; i.e., the ability to detect less salient stimuli (Siegle, Pritchett, and Moore 2014). Similarly, it has also been shown that FS-PV neurons modulate the gain in visual information processing (Atallah et al. 2012) as well as visual tuning curves (Lee et al. 2012).

The neuronal activities of FS-PV cells are also correlated with a variety of behavioral events. For example, in the motor cortex, the activity of FS-PV neurons signal cortical motor information and voluntary movement (Isomura et al. 2009). In a foraging behavior, FS-PV neurons in the ACC show a robust response to the reward port exit, and their firing rate encodes animals' foraging decision durations linearly (Kvitsiani et al. 2013). The disruption of PV-FS neuronal activities in the mouse PFC impairs social behaviors in mice (Yizhar et al. 2011). FS-PV neurons have also been shown to be critical to fear expression (Courtin et al. 2014, visual attention (Gregoriou et al. 2014), learning (Donato, Rompani, and Caroni 2013), reward-seeking behavior (Sparta et al. 2014). Many behaviors signaled by FS-PV neurons are the basic components within the dysfunction of mental disorders such as schizophrenia and autism (Marín 2012).

4.2 Long range circuitry - serotonergic system

In contrast with the local regulatory networks in the cortex, small groups of neurons send long-range projections throughout the brain and diffusely release neuromodulators such as dopamine (DA), serotonin (5-HT), and acetylcholine (ACh) in the brain. There is a rich variety of receptors for each neuromodulator, including different ligand-gated ion channels or G-protein coupled receptors (GPCRs) controlling signal transduction within post-synaptic neurons (Björklund, Hökfelt, and Swanson 1987). The dopaminergic system is the most well-understood neuromodulatory system and displays three major pathways ascending from the substantial nigra pars compacta (SNc) or VTA to the basal ganglia and cortex (Carlsson, Lindqvist, and Magnusson 1957). Functionally, dopamine is involved in motivation, reward and higher cognition and execution functions (Wise 2004, Schultz 2016). The cholinergic system has been identified

as important in brain states, attention, addiction and food intake. Projecting cholinergic neurons arise from various brain nuclei, including the basal forebrain (BF), laterodorsal tegmental areas (LDTg), and pedunculopontine tegmental areas (PPTg) (Sarter and Parikh 2005). A less explored neuromodulatory system is the serotonergic system, although many brain processes, such as memory, learning, emotion, sleep, and cognition, have been linked to it.

4.2.1 Anatomy and properties

The serotonergic neurons are located in the midbrain and brainstem regions, and those neurons are divided into two groups. There are four clusters in the superior group, including the DRN and MRN with ascending projections, and five clusters in the inferior group projecting to the spinal cord (Dahlström and Fuxe 1964). The DRN is located close to the periaqueductal gray along the midline, and it is larger rostrally than caudally. The ascending 5-HT system sends projections covering a large area of the forebrain including the VTA, HPC, SNr, NAcc, AMYG, and PFC from the superior group (Vertes 1991, Dalley and Roiser 2012. The efferent projections were recently described with increased anatomical resolution using conditional genetic methods (Muzerelle et al. 2016, **Figure 4.2.1**). Both myelinated and unmyelinated 5-HT neurons have been found in the ascending system, passing through the medial forebrain bundle (MFB). Typically each 5-HT neuron sends a large number of collateral projections to different anatomical regions (Abrams et al. 2004). The laminar distribution of 5-HT neuron terminals in the cortex is highly specific, with a high density in layers I and IV and a preference for the granular cells. Another distinction of the ascending DRN 5-HT projections are the thin fibers with many branches, whereas MRN 5-HT neurons have thick varicose fibers (Jacobs and Azmitia 1992). Within the DRN, the lateral and rostral parts project heavily to the frontal cortices and Str, whereas the caudal parts project to the HPC. Ascending DRN 5-HT neurons in the lateral DRN are ipsilateral, but ascending MRN 5-HT neurons are laterally symmetric (Törk 1990).

Serotonin was first identified in the central nervous system more than half a century ago (Amin, Crawford, and Gaddum 1954). It has been shown that DRN 5-HT neurons have not only heterogeneous topological organization and projection but also heterogeneous intracellular properties and heterogeneous post-synaptic responses. Up to now, seven classes and fourteen subtypes of receptors on the post-synaptic neurons have been identified, with 5-HT_3 receptor coupled to a ligand-gated ion channel, others as GPCRs, modulate cell signaling (Descarries, Cornea-Hébert, and Riad 2006). DRN neurons display a low firing rate during the quiet awake state (1-3 Hz) (Allers and Sharp 2003), but they can fire up to 80 Hz in response to reward delivery (Li et al. 2016). Recently, it has been shown that serotonin is also diffusely released along axons, appending more complexity on the function of 5-HT neurons (Descarries and Mechawar 2000, Fuxe

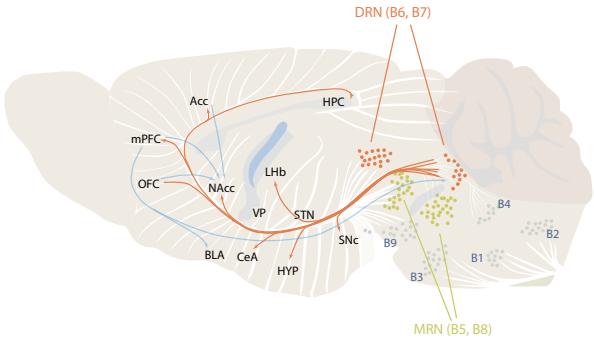

Figure 4.2.1: Schematic ascending 5-HT pathways form the DRN (orange) and MRN (green) to the forebrain in rats, major targets of the ascending 5-HT neurons including the ventral NAcc, VP, OFC, mPFC, ACC and HPC (sagital view of a rat brain).

et al. 2010). In addition to serotonin, 5-HT neurons can also co-release dopamine (Lindvall and Björklund 1974), neuropeptides, substance P, thyrotropin-releasing hormone, opioid peptides enkephalin (Hökfelt et al. 1978). Evidence of major coexistence of glutamate vesicular transporter vGlut3 recently led to further understanding of functions of ascending 5-HT neurons (Fu et al. 2010), showing a specific regulation of the VTA activities in reinforcement behaviors (Liu et al. 2014, Qi et al. 2014)

4.2.2 Behavioral functions

As ascending serotonergic projections target all parts of the brain important for decision-making, including the PFC, Str, and thalamus, it is not surprising that the manipulation of serotonin levels in the CSF or DRN 5-HT neuronal activities alters decision processes in many manners (Doya 2008). Tryptophan depletion in healthy human subjects impairs their attention control as well as reinforcement learning processes (Rogers et al. 1999b). Similarly, administration of SSRI impairs the ability of probability learning, increases the response latency (Chamberlain et al. 2006) and increases the effort subjects are willing to exert for reward (Meyniel et al. 2016). Both patients with chronic addiction to amphetamine and healthy volunteers subjected to acute 5-HT depletion exhibit decision-making at a suboptimal level and deliberate longer time before making a choice, similar to what is seen in patients with the OFC damages (Rogers et al. 1999a). Inflexible behaviors can also be observed with 5-HT depletion in primates, evident as increases in preservative responding without affecting stimuli discrimination (Clarke et al. 2004). Functional imaging studies have shown that increased neuronal activities in the Str encode the time scale of reward prediction, and such activities are regulated by the 5-HT system (Tanaka et al. 2007).

Studies in animal models have distinguished the roles of the dopaminergic system and the serotonergic system. Dopaminergic neurons are required for both effort and delay, but 5-HT neurons are only neces-

sary for the delay in a cost-benefit decision paradigm (Denk et al. 2005). 5-HT release from the terminals of DRN 5-HT neurons in the rat PFC is critical in learning a goal-directed behavior and cognitive flexibility (Plasse et al. 2007). Early hypotheses suggested that phasic DRN 5-HT neuronal activities encode both current prediction error and future aversive stimuli (Daw, Kakade, and Dayan 2002). More recently, many studies have illustrated a complex picture of potential roles of DRN 5-HT neurons. Miyazaki and colleagues used extracellular recordings in behaving animals to show that DRN neurons, potentially 5-HT neurons, respond strongly to waiting (Miyazaki, Miyazaki, and Doya 2011). However, their activities can also encode a variety of other behavioral events, including actions such as nose-poke, movement, and reward (Ranade and Mainen 2009). Optogenetic activation of DRN 5-HT neurons increases patience for receiving reward (Miyazaki et al. 2014, Fonseca, Murakami, and Mainen 2015), although they do not to alter subjective timing function in the animals (Clark et al. 2005, Heilbronner and Meck 2014, Ho et al. 1996). DRN 5-HT neurons are also linked to the reward signal in the OFC (Zhou et al. 2015). Direct stimulation of DRN 5-HT neurons lead to strong reinforcement learning (Liu et al. 2014), transient inhibition and long-term facilitation of locomotion (Correia et al. 2017). Moreover, the recent studies revealed additional roles of DRN 5-HT neurons in different behavioral events including encoding reward (Li et al. 2016) and predicting the internal driving state (Cohen, Amoroso, and Uchida 2015).

"In a dream it's typical not to be rational."

John Forbes Nash, Jr.

5

Mental Disorders and Decision Dysfunction

Among the top ten causes of disability, five are mental disorders. Mental disorders comprise 7.4% of global disability-adjusted life years, accounting for 183.9 million people in 2010 (Murray et al. 2012). In the World Economic Forum 2010, it was estimated that the cumulative economic output loss due to mental disorders in the next 20 years could sum up to $16 trillion, equivalent to 25% of the global GDP in 2010 (Whiteford et al. 2013). Nevertheless, the cost calculation fails to capture social burdens associated with mental disorders. The global efforts fighting against mental disorders come from public health, medical treatment, and basic neuroscience research collectively.

There exist many forms of mental disorders, hitting people by paralysis of cognitive functions, the frustration of mood, panic, and anxiety. Mental disorders share common signs and symptoms, and the main focus of science and research is to address the symptoms. Genomic and brain imaging in the past decade have enabled significant advances in the upstanding of mental disorders, and examination of neural mechanisms in the coming decade will allow us to fractionate symptoms of mental disorders into neuroscientific components. In this chapter, I will focus on the fundamental understanding of brain functions, summarize neuroscientific findings of the three most common psychiatric disorders, and discuss the mechanisms and consequences of disrupted biological building blocks and their impact on human behaviors.

5.1 Attention Deficits Hyperactive Disorder

ADHD, according to a recent meta-analysis, is a brain disorder that affects 3-4% of children, with higher frequency in boys than girls (Polanczyk et al. 2015). The hallmarks of a person with ADHD include (**a**) a lack of sustained attention or focus; (**b**) hyperactivity with constant and excessive talking or locomotion; and (**c**) impulsivity including a failure to consider long-term consequences but instead acting on urges and in haste. People with ADHD typically exhibit one or two symptoms occurring with a high frequency, interfering with their social function at school or in a job or other activities (American Psychiatric Association 2013, World Health Organization 1992). ADHD is highly heritable, with multiple genes and environmental factors associated (Thapar and Cooper 2016).

5.1.1 Symptoms and mechanisms

People with inattention often overlook or miss details while performing some work, lack sustained focus on tasks, conversations, or reading, and cannot follow through with orders or guidance; however, they easily get distracted or sidetracked. Thus, they have difficulties in organizing activities and tasks, fail to track necessary things or activities in a task, show poor performances as regards time management, deadlines, the preparation of reports, or reviews of lengthy papers. People with hyperactivity-impulsivity exhibit impatience while seated and display fidgets and squirms, and they often leave their seats unexpectedly. They often cannot engage in activities or tasks quietly but are constantly driven by an urge to dash into situations restlessly. The problem with waiting is another trait, including difficulties in waiting for his or her turn, answering before the question has been finished, and interrupting and intruding into the conversations or activities of others.

Although ADHD has rapidly increased in prevalence, disrupts many abilities, and shows persistent adverse effects in adult life, research has failed to generate a single theory of its pathogenesis (Castellanos and Tannock 2002). Instead, neuropsychological endophenotypes such as deficits in cognitive functions, response inhibition, executive control, and planning and working memory have been reliably identified and widely used in diagnosis (Thapar and Cooper 2016). A variety of brain regions have been associated with ADHD through neuroimaging (Giedd and Rapoport 2010). Children and adolescents with ADHD show decreased function in the inferior PFC, basal ganglia, cerebellum and parietal cortex (Rubia et al. 2010). There are other lines of evidence showing deficits in some of the symptoms of ADHD from patients with brain damage, such as deficits in the orienting system (Robertson et al. 1998). Animal models, on the other hand, can recapitulate specific endophenotypes of ADHD and allow direct manipulation of neural circuitry and modification of behavior (Purper-Ouakil et al. 2011).

5.1.2 Prefrontal cortex and top-down control

Top-down attention is driven by factors such as our goal, expected utility, and knowledge, whereas bottom-up attention reflects the reflexive response of our sensory system (Corbetta and Shulman 2002). In goal-directed behaviors, top-down attention is required for the subjects to orient their focus toward salient stimuli and away from distracting stimuli. Therefore, irrelevant information is suppressed in the sensory systems in the goal-directed behavior (Kastner and Ungerleider 2000). Mental disorders share attention deficits to a large degree, and the study of pathology gives researchers hint of the link between cognitive dysfunction and brain regions, which later lead to findings in mechanisms. Patients with schizophrenia show impairment in top-down control of attention (Gold et al. 2007), and patients with borderline personality disorder exhibit similar deficits (Clarkin and Posner 2005). Therefore, attention control is used as a reliable measurement in the diagnosis of a variety of mental disorders, and animal models of mental disorders (Lustig et al. 2013). Luckily, the deficits are not always irreversible; for example, a brief period of training in an attention task can improve cognition performance in children (Rueda et al. 2005).

Feedforward visual sensory processing is modulated by attention (Zhang and Luck 2009), and the PFC has been shown to be one of the critical regions in top-down control of memory retrieval (Tomita et al. 1999). Using fMRI, the human PFC has been shown to play a vital role in a selective attention process in a delayed-recognition task. Such function is confirmed by inhibiting the PFC with 1 Hz repetitive TMS before attention (Zanto et al. 2011). In addition, the PFC has been shown to bias stimuli-driven responses in the visual cortex but, inhibiting the sensory motor cortex, serves as a central computation unit in assigning priorities of different tasks (Liu et al. 2016). Recently, ventral medial PFC projections to the basal medial AMYG has also been shown to regulate anxiety states and stress-induced anxiety (Adhikari et al. 2015). In contrast, ventral medial PFC projections to the HPC selectively recruit a sparse population of neurons for pattern and salience storage during memory retrieval (Rajasethupathy et al. 2015). Furthermore, the PFC has been shown to be essential in cognitive control through inhibition of automatic functions, rational reasoning, and modulation of cognitive flexibility (Diamond 2013). There exist many parallel hypotheses explaining the PFC top-down controlling mechanisms; a study showed the PFC oscillation signals top-down attention, but the parietal oscillation signals bottom-up attention (Buschman and Miller 2007). Largely based on recordings of animals during attention process, Engel and colleagues suggested an active top-down regulatory mechanism using oscillation and long-range synchrony (Engel, Fries, and Singer 2001).

5.2 Depression

Depression and ADHD share symptoms of low mood or low self-esteem, and ADHD medication is associated with reduced risks of depression (Chang et al. 2016). However, depression is the most disabling disorder around the globe (Murray et al. 2012), with an average prevalence of 8-12% during the lifetime. Depression severely disrupts people's daily activities including eating, working, or sleep, by altering how people feel, think, and behave. People, thus, may withdraw from activities that were gratifying, start overeating or fast, and experience hardship in focusing, decision-making, and many other problems. Several different types of depression have been identified, such as major depression, persistent depressive disorder, psychotic depression, postpartum depression, and bipolar disorder. The severity, frequency, and duration of symptoms of depression may vary considerably among people depending on their particular illness, as well as within one person at different stages. Both heritable and nonheritable factors, such as genetics, brain biology, and environmental triggers, are strongly associated with depression.

5.2.1 Symptoms and mechanisms

Current diagnostics of depression largely rely on symptoms (American Psychiatric Association 2013, World Health Organization 1992). People with depression may experience some signs and symptoms during most of the day, nearly every day for longer than two weeks. The signs or symptoms include (**a**) persistent anxiety and sad or "empty" mood; (**b**) hopelessness or pessimistic feelings; (**c**) irritability; (**d**) helpless, worthless or guilt feelings; (**e**) anhedonia or loss of pleasure; (**f**) fatigue and low in energy; (**g**) slowness in moving or talking; (**h**) restlessness or impatience while seated; (**i**) difficulties in focusing on tasks or making decisions; (**j**) disrupted sleep or eating; (**k**) suicide thoughts or attempts; (**l**) pains without physical cause.

Given our limited knowledge of the brain regions and neural circuits we possess, adding that we know the heterogeneity of depression, it is likely that distinct brain regions are specific to each subtype of depression. The DRN was one of the earliest identified regions tha could be involved in depressive symptoms. Non-specific monoamine drugs or 5-HT specific drugs have been used as conventional antidepressants for more than half a century, and they're still the most effective treatment. Patients carrying a polymorphism in the 5-HT transporter show robust correlation to the symptoms, diagnosis of the disorder, and suicide (Caspi et al. 2003). They also have a reduced volume of gray matter in the cingulate and amygdala region, suggesting a role in emotion regulation (Pezawas et al. 2005). A range of different brain regions, including the hippocampus and PFC, have also been linked to depression and a range of coexisting symptoms such as cognitive deficits and violence (Fazel et al. 2015)

By using a voltage sensitive dye in neuroimaging, the hippocampal dynamic is showed as a robust predictor of antidepressant treatment in states of depressive symptoms (Airan et al. 2007). Optogenetic activation of DA neurons projecting to the NAcc induced susceptible phenotype of social-defeat stress behavior. Inhibition of the same projection DA neurons induces resilience of the same behavior. Interestingly, only inhibition of the VTA–mPFC projection promotes susceptibility of social-defeat stress behavior (Chaudhury et al. 2013). *In vivo* recordings have shown that activation of DA neurons in the VTA-NAcc pathway altered neural coding in the NAcc and reduced expression of depression-like behavior (Tye et al. 2013). A similar antidepressant effect can be achieved by activation of the mPFC (Covington et al. 2010), and more specifically, the PFC to DRN projection is sufficient to produce a rapid and profound antidepressant effect (Warden et al. 2012). Recently, using fMRI in awake rodent and optogenetic stimulation makes it possible to simultaneously record and analyze neuronal activities from all the brain regions while stimulating the VTA DA neurons (Ferenczi et al. 2016).

5.2.2 Glutamate hypothesis

Although monoamine systems such as the ascending DRN 5-HT population or ascending noradrenaline neurons is proven important in depressive disorder; clinical studies and practices also suggest a predominant role of glutamate transmission Sanacora, Treccani, and Popoli 2012. As glutamate is the dominant neurotransmitter, its transmission plays a central role in mediating the complex emotional/cognitive changes associated with depression. Using ketamine, a non-competitive NMDAR antagonist, although not as first line treatment, it shows a profound and rapid effect in patients with treatment-resistant depression (10%-20% of total patients, Trullas and Skolnick 1990). Unlike the monoamine antidepressant, ketamine acts within hours, showing a significant improvement of symptoms of depression. Thus it's also used as a common treatment for other mood/anxiety disorders. Patients with depression have an elevated cerebrospinal fluid (CSF) concentration of glutamate (Kim et al. 1982). The concentration linearly predicts the severity of depression (Mitani et al. 2006), and selective serotonin reuptake inhibitors (SSRI) such as fluoxetine or citalopram-treated patients exhibit a decrease of CSF glutamate concentration (Küçükibrahimoğlu et al. 2009). The dysfunction of the glutamatergic system has been shown in the cortical-limbic areas in depressed subjects (Castillo et al. 2000, Konarski et al. 2008). Removing of NMDAR shows several cognitive deficits including working memory, fear expression and anxiety (Carlén et al. 2012, Korotkova et al. 2010). Ketamine has also been shown to activate mTOR signaling cascade and protein synthesis in the synapse mediated by glutamate and, later, by brain-derived neurotrophic factor (BDNF) (Duman et al. 2012).

5.3 Impulsive Disorder

Impulsive disorders encompass a broad spectrum of mental disorders, including pathological gambling, intermittent explosive disorder, pyromania, and borderline personality disorder (Hollander and Evers 2001). Impulsive disorders share a core symptom of high impulsivity, also present in other mental disorders such as ADHD and mania. People with high impulsivity exhibit a lack of the vital ability to hold back reflexive reactions and act from urge or desire, therefore, failing to deliberate and reflect on the future events with potentially better outcomes (Bari and Robbins 2013). In a large cohort study, childhood impulsiveness score has been shown to be a robust predictor of socioeconomic status in the adult life (Moffitt et al. 2011). Impulsive behavior has long been studied in both humans (Patton, Stanford, and Barratt 1995) and rodents (Dalley and Robbins 2017), and it has been demonstrated that impulsive behavior is not unitary but multifaceted (Bari and Robbins 2013).

5.3.1 Symptoms and mechanisms

Different impulsive disorders exhibit different symptoms. People with intermittent explosive disorder may feel energetic and have racing thoughts, accompanied by persistent outbursts or explosive periods. An individual with pathological gambling may be preoccupied with gambling, persistently planning to get more money to gamble, chase losses, gamble to escape from anxiety, depression, or guilt, and increase gambling sum to receive thrill. An individual with eating disorders may suffer from emotional, physical, and self-esteem disturbances, showing persistent fear of weight gain, loss of judgment during fasting, frequent consumption of large amounts of food, strong guilt about binge eating. An individual with borderline personality disorder is emotionally unstable, often has intense relationships with others, and feels an impulse to harm his/her body.

There is no single theory accounting for the cause of impulsive disorders. Impulsive behaviors may have been evolutionarily advantageous when our human ancestors lived in the wilderness, as they can provide a fast response to danger or reward, thus saving the individual from predators or hunger. However, in today's modern society, we all process a large quantity of information, and the time pressure on our actions or decisions often lead to premature responses and undesirable consequences. Researchers have been trying to understand impulsivity since the behavior was described. Mischel and his colleagues, in 1972, tested children's preference for an immediate reward of one marshmallow versus two marshmallows after several minutes (Mischel, Ebbesen, and Zeiss 1972). This group of behaviors was later partitioned into basic components (Patton, Stanford, and Barratt 1995). The Barratt Impulsiveness Scale, BIS-11 (Barratt 1959), is an international standard for assessing impulsiveness in humans. According to Patton and colleagues,

impulsiveness can be fractionated into several factors, including (**a**) attention, (**b**) motor, (**c**) choice, and (**d**) cognition. Motor refers to acting on the spur of the moment. Choice refers to planning for future consequences and postponing gratification, whereas cognition refers to racing thoughts or appreciation of mental tasks. Although different classifications of impulsive behaviors vary from basic research to clinical practice, they all share the same components of impulsive action and impulsive choice (Dalley and Roiser 2012, Hamilton et al. 2015).

Human imaging studies can provide correlations between brain areas and impulsivity. A study using a monetary reward and fMRI has revealed that the vStr, medial OFC, mPFC, and PCC are activated for the immediate reward, whereas such regions as the dlPFC, vlPFC, and SMA respond to the decision process (McClure et al. 2004). Patients with the vmPFC lesion exhibit deficits in decision making by persistently choosing a smaller and sooner reward (Bechara, Tranel, and Damasio 2000). Animal studies typically utilize lesions in specific brain regions to confirm a causal relationship between anatomical regions and a behavioral output. Disrupted vmPFC function leads to an increase of impulsive action but does not affect delay discounting in rats (Feja and Koch 2014), whereas lesions in the NAcc induce persistent impulsive choice and locomotor hyperactivity in rats (Cardinal et al. 2001). Furthermore, using an RNA interference to disrupt GABA gene in NAcc is sufficient to increase motor impulsivity, suggesting an essential role of the NAcc GABA signaling in impulsive choice (Caprioli et al. 2014). Belin-Rauscent and colleagues showed that lesions in the AIC lead to increased impulsive action measured as increased premature responding (Belin-Rauscent et al. 2016). By altering the DA signaling, Stopper et al. 2014 has shown that inhibition of VTA DA neurons using LHb and RMTg stimulation shifts the animal's preference for a larger reward; however, direct stimulation of VTA makes subjects more risk-taking.

5.3.2 Implication of the serotonergic system

Serotonin and DRN 5-HT system have long been associated with impulsive action and impulsive choice (Dalley, Everitt, and Robbins 2011, Soubrié 1986, Asberg, Träskman, and Thorén 1976). Acute tryptophan depletion leads to increased delay discounting and thus increased impulsive choice (Schweighofer et al. 2008), as well as an increase of locomotion activities (Walderhaug et al. 2002). Tryptophan depletion also disrupts learning of stimulus-driven reward learning Rogers et al. 1999b, emotions, response to aversive stimuli and compulsive behaviors (Cools, Roberts, and Robbins 2008). Lesions of ascending DRN serotonergic pathways lead to altering subjective time perception (Morrissey et al. 1994). However other studies cannot identify any effect in subjective timing (Clark et al. 2005, Heilbronner and Meck 2014, Ho et al. 1996).

It has also been a paradox and a substantial challenge to pinpoint the functions of the DRN 5-HT system in impulsive behaviors given its complexity of topological projections, variety of post-synaptic receptors, and auto-receptors (Cools, Roberts, and Robbins 2008). Manipulation of the serotonergic system in animals has produced mixed results in impulsive action (Humpston, Wood, and Robinson 2013, Tsutsui-Kimura et al. 2009, Winstanley et al. 2004) and impulsive choice. Some of the studies show an increase of serotonin level can decrease the degree of impulsive choice (Crean, Richards, and Wit 2002, Fairbanks et al. 2001, Harrison, Everitt, and Robbins 1997, Schweighofer et al. 2008, Thiébot, Martin, and Puech 1992), whereas the others cannot show any significant change of animals' decision preference (Baarendse and Vanderschuren 2012, Evenden and Ryan 1996, Winstanley et al. 2004).

Waiting for reward is one of the recently identified functions for DRN 5-HT neuronal activity (Miyazaki, Miyazaki, and Doya 2011), and it can potentially play a key role in impulsive behaviors as the ability to wait can predict better performance in both impulsive action and impulsive choice. This correlation was later confirmed by driving the same population directly in behavioral tasks that required waiting (Fonseca, Murakami, and Mainen 2015, Miyazaki et al. 2014). However, direct driving of the DRN 5-HT neurons does not result in any reinforcement behaviors, which could serve as an additional pillar in impulsive behaviors. On the contrary Fonseca, Murakami, and Mainen 2015, other groups have shown DRN 5-HT neurons have strong reinforcement effect through the action of glutamate (Liu et al. 2014, McDevitt et al. 2014). Recently, using optical imaging, a large portion of the DRN 5-HT neurons have been confirmed to respond robustly to reward delivery in a foraging task but also exhibit a heterogeneous response, such as a suppression of activity upon reward delivery (Li et al. 2016). Current evidence suggests DRN 5-HT neurons do not simply regulate impulsive behaviors via modulating waiting, time perception, or reward; they rather monitor the overall cost-benefit status through integral functions yet to be explored (Luo, Li, and Zhong 2016, Cohen, Amoroso, and Uchida 2015).

"One of the first rules of science is if somebody delivers a secret weapon to you, you better use it."

Herbert A. Simon

6 Aim and Methods

Exciting technologies such as light-sensitive proteins, enable us to explore the complex structure and functions of the brain, a structure with billions of neurons and quadrillions of connections. Optogenetics made it possible to selectively target a subpopulation of neurons or a specific part of one circuit of the brain in behaving animals. Optical imaging allows us simultaneously record the activity of a large population of neurons *in vivo*, and to thus probe the network dynamics and neural coding mechanisms. The combination of new technologies with classical behavioral paradigms brings new insights into fundamental principles in how the brain functions.

6.1 Aim

This thesis focuses on how neural circuitry can shape animal behaviors in different phases of decision-making. As it is still impossible to understand the decision-making process in one single experiment, we used a variety of behavioral paradigms specific to attention, depressive-like behaviors, anhedonia, impulsive action, or impulsive choice. The general aim is to take advantage of novel methods, scratch the surface

of the underlying principle, and further our understanding of the different functional aspects of the most complex organ we know. More concretely, in the following three studies, we aimed to:

I. To understand the neuronal activities and functional relevance of the mPFC FS-PV cells during a behavioral task requires top-down attention. Specifically, the study aims to (**a**) reveal the signatures of FS-PV cells in top-down attention, (**b**) understand behaviors of the mPFC neural circuit, (**c**) reveal the computational mechanisms of the mPFC pyramidal neurons regulated by FS-PV, and (**d**) examine the causal relationship between the mPFC FS-PV neurons and top-down attention behaviors.

II. To understand the role of NMDAR on FS-PV cells in depressive-like behavior. More specifically, we aim to (**a**) understand if NMDAR-dependent neurotransmission in mPFC FS-PV cells is necessary for the fast-acting antidepressant effect of NMDAR antagonists such as ketamine and MK801 and (**b**) if NMDAR-dependent neurotransmission in mPFC FS-PV cells is functionally relevant to anhedonia in depression.

III. To understand the role of the long-range ascending DRN 5-HT modulation system in control of decision-making in the context of impulsivity. Specifically, the study aims to (**a**) target the DRN 5-HT neurons selectively in the rat, (**b**) set up human analogous operant behavioral tests for impulsive behavior, (**c**) examine the causal relationship between the DRN 5-HT neuronal activity and impulsive action, (**d**) examine the causal relationship between the DRN 5-HT neuronal activity and impulsive choice, and (**e**) study the real-time DRN 5-HT neuron activity in behaving animals in the impulsive action task.

6.2 Methods

In this thesis, we used both mouse models and a rat model. Mouse models are widely used because of the leading advances in genome modification and a versatile of tools using the genetic engineering technologies. Many human disease models are well established using mouse models for the understanding of pathophysiology, development, cell, and molecular biology. Single genes can be selectively removed, particularly in the areas of psychiatry. Many genes have been implicated in different mental disorders, encoding receptors, or neuronal signal transmission. Manipulation of expression of these genes such as knockout creates symptoms closely resembling human mental disorder and therefore makes it possible to identify the genetic cause of a given disease (Gottesman and Gould 2003).

On the contrary, rat models are lagging behind in the usage of the genetic toolbox. However, they have long been the preferred subject in many experimental settings in neuroscience. Because genetically modified rat models are underdeveloped, application of optogenetics or optical imaging is more frequently in the mouse models (Zalocusky and Deisseroth 2013). On the other hand, for reasons such as their larger body size, they can not only easily carry heavier and bulkier hardware but also enable more precise targeting

and read-out neuronal activities from specific anatomical regions. The most valuable use of the rat models in neuroscience has been the development, optimization, and validation of a broad array of complex behavioral tasks in psychology (Skinner 1963). Rat paradigms are also well established and heavily applied in pharmacotherapies analogous human cognition and psychiatry (Robbins 1998).

6.2.1 Behaviors

Mouse 3-choice serial reaction time task requires animals to allocate attention to the spatial position where visual stimuli would appear (Bari, Dalley, and Robbins 2008). The operant chamber (CeNeS, UK) was modified from a 9-CSRTT where LED lights were mounted as visual stimuli, and IR sensors were equipped to detect animals' nose-poke behavior. The animals were handled for several consecutive days before training started, and then they were trained in a successive approximation reinforcement schedule for the target behavior in 6 discrete stages. In the target behavior, the visual stimuli were presented pseudorandomly with a delay of 3, 4, or 5 seconds, and the intertrial interval (ITI) was pseudorandomly assigned to each trial in the same task. The limited hold (LH, 5 seconds) defines the time window within which animals need to respond after the cue onset for reward delivery; unsuccessful nose-poke within the time window was registered as omission, and nose-poke before visual stimuli was registered as premature response.

In the target behavior, the duration between nose-poke to report visual stimuli and nose-poke to reward port as reward latency was measured. All error responses, including error nose-poke, premature nose-poke or omission would generate a 5-seconds timeout when no action can lead to any events in the operant chamber. Correct report to visual stimuli allow animals to retrieve sucrose water (15%) reward, and nose-poke into the reward port initiates a pseudorandom ITI and later a new trial. A series of actions are required for the animal to receive the reward, start with nose-poke into the reward port, consume the reward, allocate attention to the position of potential visual stimuli, restrain action before visual stimuli appear, and nose-poke within 5 seconds after the visual stimuli are presented. Additional IR sensors were set in the operant chamber for adaptation of the behavioral paradigm to animals with a fiber optic implant or microdrive implant. After the modification, animals received enough time to turn around and face the visual stimuli even they were carrying bulky implants. (detailed **Methods** can be found in **Paper I**)

Mouse forced-swimming test is a behavioral paradigm in which learned helplessness is induced in a transparent acrylic cylinder with 1800 ml of water at 25 ± 1°C (Slattery and Cryan 2012). Each session lasts 6 min when mice could neither reach the bottom nor the edge of the cylinder. Different behavior statuses were scored; active swimming is when the subject swims within the cylinder, and passive floating was the time when the subject was immobile. Typically, the antidepressant-like response could reduce immobility

in the paradigm. The FST started 30 min after the intraperitoneal (i.p.) injection of saline, ketamine, or MK801, then repeated at 24 hours, 48 hours, 72 hours, 96 hours, and 240 hours later. After each experiment, animals were rescued from the cylinder, dried, and returned to their home cages. (detailed **Methods** can be found in **Paper II**)

Mouse sucrose preference test examines animals' interest in seeking outmore rewarding sucrose water versus plain water, and it is typically used as a model for mental disorders with affective symptoms (Strekalova et al. 2004). It was started 24 hours after a drinking pre-test in a two-bottle paradigm for all experiment animals. In the test, animals were free to choose between 2% sucrose water in one bottle and plain water in another for 72 hours without any restraint or food deprivation. The bottle positions were counterbalanced for removal of any bias of bottle location. Possible water leakage, temperature change, air pressure change were also controlled. The total intake of sucrose water and plain water was measured after the experiment, and the percentage of sucrose water intake was then calculated by dividing the total amount of liquid intake. (detailed **Methods** can be found in **Paper II**)

Rat fixed interval task is measuring the response rate during a fixed delay period as an index of impulsive actions (Mahoney, Silveira, and Olmstead 2013). It requires an animal to hold/restrain their premature action during a fixed delay and nose-poke afterward in responding to a visual stimulus to receive 10% sucrose water reward (200 μl). The animals were pre-trained to learn how to operate the chamber to initiate a trial or receive the reward with a shaping procedure with Pavlovian conditioning. They were then trained to learn different fixed delays (8 seconds, 16 seconds or 32 seconds) in each of the three reward delivery ports. After animals were fully trained, they could start a trial by nose-poke into the port with initiation cue on the rear wall. Then one of the three front ports will present a visual stimulus as the target cue, and the target cue would only turn off upon the nose-poke into the port after the fixed delay has elapsed with sucrose water reward delivery. The ITI started after reward delivery with a random duration following a uniform distribution (μ = 144 second). The port location of fixed delays was counterbalanced between subjects, and trials were organized in blocks for optogenetic stimulation and counterbalancing. (detailed **Methods** can be found in **Paper III**)

Rat time-discounting choice task is a forced choice paradigm that requires animals to respond to a smaller sooner (SS, 200 μl) reward or larger longer (LL, 600 μl) reward respectively (Roesch, Taylor, and Schoenbaum 2006). The animals were pre-trained to learn how to operate the chamber to initiate a trial or receive a reward with a shaping procedure with Pavlovian conditioning. Later, a successive approximation reinforcement schedule with four discrete stages was used to train animals for learning of two distinct sample cues indicating SS or LL reward. In the target behavior, SS trials (signaled by one yellow LED light) had a 1-second delay, and LL trials (signaled by two white LED lights) had variable delays (2, 5, 10, 20, 30, 40,

or 60 seconds). Only one configuration was presented in each block of 10 trials. Animals initiated one trial by nose-poking the central front port; then one of the side LED cues would light up, presenting either an SS or an LL trial. The central front port will present the same LED pattern as the target. On the other side port where target cue is not presented, a distractor will present show a wrong LED pattern. Nose-poke into the distractor port will abort the current trial and register an error response. Error trials comprise of incorrect trials in which animals performed an error response immediately after initiation, whereas impatient incorrect trials indicate they gave up after the first correct nose-poke. After the reward delivery or error response, the ITI will start with a random duration following a uniform distribution (μ = 144 second). (detailed **Methods** can be found in **Paper III**)

6.2.2 Surgery, virus injection, implants

Standard stereotaxic procedures (quintessential injector: Stoelting) were used for viral injections with the body temperature carefully monitored. Subjects were first anesthetized with isoflurane (2%) in O_2; then a small craniotomy was made on the animal skull for injection (32 gauge Hamilton syringe) of 0.7 μl of ChR2, SwiChR, Jaws or eYFP carrying viruses, targeting various anatomical regions including the PrL, or DRN. The injection was done at 0.1 μl/min, followed by 5 min waiting before the syringe can be slowly retracted. Either microdrives (In house built, 2 cm height, 1.5 cm diameter, 2 grams, **Figure 6.2.2b**) were implanted for the chronic recordings, or fiber optic (mice: Φ 200 μm core, 0.22 NA, 10°angle; rats: Φ 300 μm core, 0.37 NA, 20°angle, Thorlabs, **Figure 6.2.2d**) were implanted for optogenetic stimulation. For implantation on the rat skull, bone screws (mice: n = 2; rats: n = 4 - 5, Fine Science Tools) were also used for fixation of the implants with light curing dental cement (Ivoclar Vivadent) (**Figure 6.2.2a**). Analgesic (buprenorphine 0.1 mg/kg s.c.) was used for post-surgery pain relief.

6.2.3 Optogenetics

Genetically encoded opsins derived from microbial organisms (Nagel et al. 2002) enable fine control of neuronal activities in a specifical neuron population restricted by genetic profile or topographical location. The selectivity of optogenetic control was not possible using traditional electrical stimulation method (**Figure 6.2.1a**). Channelrhodopsin-2 (ChR2) is the first microbial opsin used in mammalian cells (Boyden et al. 2005) with non-selective cation channels. Activation of ChR2 using blue lights can open the channel and lead to depolarizing of the neurons that express the opsin (**Figure 6.2.1b**, *left*). Inhibitory opsins such as NpHR or Jaws use chloride pump or proton pump to hyperpolarize the neurons with opsins expressed (**Figure 6.2.1b**, *middle*). Also, opsins such as OptoXR for biomechical control respond to light

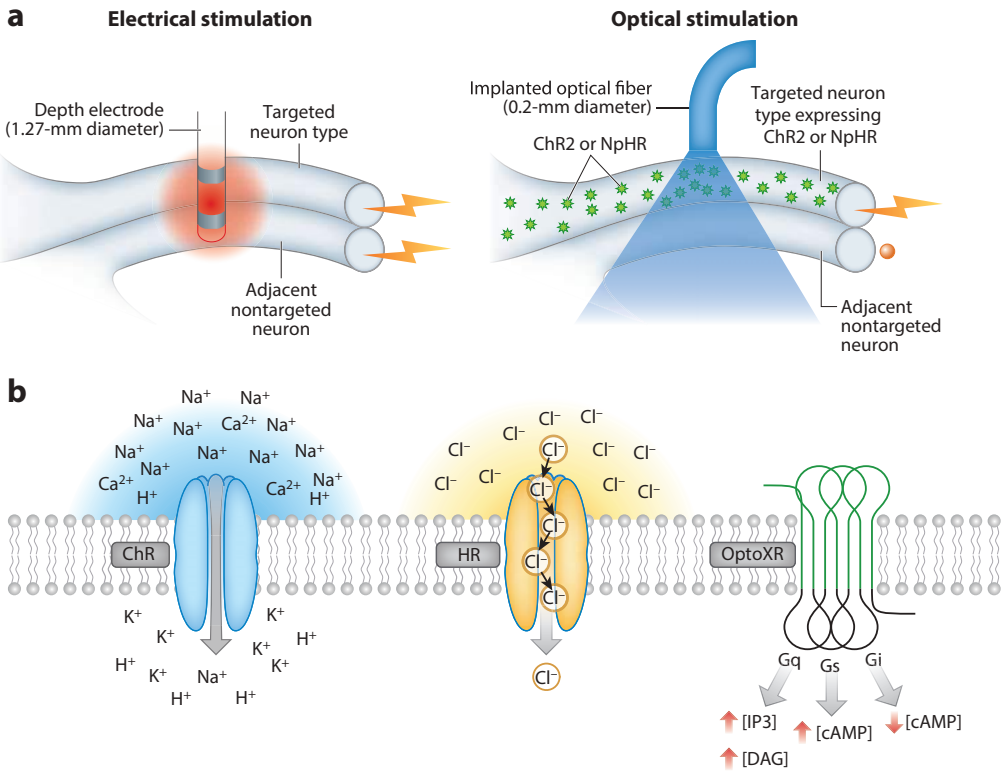

Figure 6.2.1: **a** Electrical stimulation modulates the brain activity ubiquitously at the local level. Genetically restricted optogenetic manipulation allows selective manipulation of specific neuron type in the heterogeneous brain tissue. **b** A large variety of optogenetic constructs are available for neural activity control, including light-gated cation channels in the ChR-family (left), light gated chloride pumps in the HR-family (middle) as well as intracellular signalling cascads modulators in the OptoXR family (right) (Modified from Warden, Cardin, and Deisseroth 2014 with permission).

and activate intracellular signalling cascades (**Figure 6.2.1b**, *right*).

Mice (n = 5) injected with AAV-DIO-SwiChR-EYFP or AAV-DIO-ChR2-mCherry and bilateral implanted with fiber optics were resumed training in the 3-CSRTT task 7 days post-surgery. Light stimulation was delivered through a patch cable (**Figure 6.2.2b**) with optic rotary joint (FRJ_1×1_FC-FC, Doric Lenses) from a blue diode laser (MLDTM 473 nm, Cobolt) or red diode laser (MLDTM 638 nm, Cobolt) from control software LabView. For optogenetic inhibition of the mPFC FS-PV neurons in the 3-CSRTT, brief blue light pulses (0.5, 1, or 2 seconds) were used to activate the neurons and red light (1 second) for SwiChR termination; a total of 4,362 trials were collected from 5 animals. For optogenetic activation of the mPFC FS-PV neurons in the 3-CSRTT, 5 ms blue light pulses were delivered at a range of frequencies

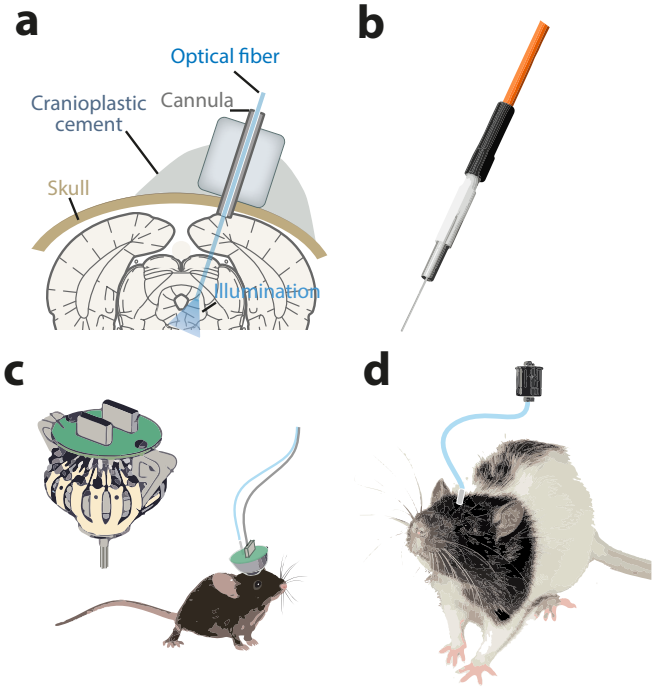

Figure 6.2.2: **a** Fiber optic implantation and fixation on the skull with cranioplastic cement. **b** Ferrule for implant and mating sleeve for coupling of light source. **c** Microdrive with movable tetrodes for extracellular recordings in freely behaving mice. **d** Freely behaving rats with fiber optic implants and rotary joint.

(1, 5, 10, 20, 30, 40, 60 Hz) in each session, and a total of 10,302 trials were collected from 5 animals.

Rats (Fixed interval task: n = 7; time-discounting choice task: n = 8) injected with AAV-DIO-ChR2-mCherry, AAV-DIO-Jaws-eYFP, or AAV-DIO-eYFP, and implanted with fiber optic were resumed training in the FI task or the TDC task 14 days post-surgery. Light stimulation was delivered through a patch cable (**Figure 6.2.2b**) with optic rotary joint (FRJ_1×1_FC-FC, Doric Lenses) from a blue diode laser (MLDTM 473 nm, Cobolt) or a amber DPSS laser (DPSS 593 nm, Changchun New Industries) from control software Arduino. For optogenetic inhibition of DRN 5-HT neurons in the FI task or the TDC task, amber light was constantly on from the trial initiation until the trial was ended. For optogenetic activation of mPFC FS-PV in the FI task or the TDC task, 5 ms blue light pulses were delivered at a range of frequencies (20 or 60 Hz) in each session. Laser stimulation was counterbalanced by stimulation every second block. A total of 3,838 trials were collected in the FI task, and 14,969 trials were collected in the TDC task.

6.2.4 Extracellular recording

PV-Cre mice (n = 3) were fully trained and implanted with microdrives. Then, they were allowed to recover for seven days before the training of in the 3-CSRTT resumed (**Figure 6.2.2c**). After all animals had been retrained for 7-14 days with performance satisfying the target criteria, the neural activity was recorded using

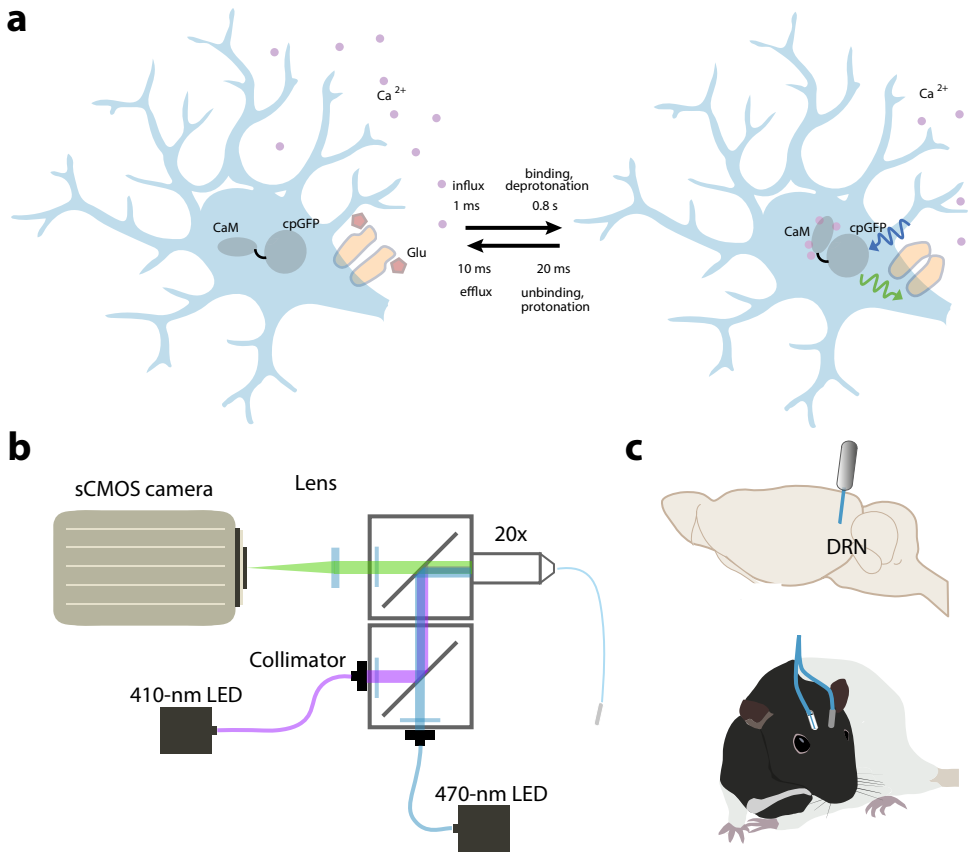

Figure 6.2.3: a GCaMP6 series calcium indicator. **b** Fiber photometry acquisition diagram system used for simultaneous calcium signal measurement. **c** Schematic fiber photometry implant for real-time calcium signal recordings in rat.

Digital Lynx 4SX acquisition system and the Cheetah software for 54 sessions. A total of 3,857 trials were recorded while each tetrode was able to move individually ventrally 20-40 μm after the experimental end point. Single unit activities were amplified and filtered with a bandpass of 600-6,000 Hz, then digitized at 32 kHz, whereas local field potentials (LFPs) were recorded from one of the single electrodes of the tetrodes, then filtered with a bandpass of 0.1-500 Hz. Before the experimental end point, lesions were made at the final depth of the electrodes for histological examination later.

6.2.5 Optical imaging with genetically encoded indicator

Instead of directly recording of the electrophysiological properties of neurons during the behavior, the genetically encoded indicators, such as the calcium indicator, enable the visualization of neuronal activity in a genetically defined neuronal subtype, and this further allows the study of neural dynamics during development, learning or progress of diseases (Dana et al. 2016, Peters, Chen, and Komiyama 2014, Ziv et al.

2013). More importantly, it allows either high-resolution optical imaging of subcellular activity (Sofroniew et al. 2016), the imaging of thousands of neurons simultaneously (Stirman et al. 2016), or fast and collective recording of population activity with fiber photometry (Kim et al. 2016a). Spikes can typically be detected and characterized using signal detection theory by the metric *d'* (Wilt, Fitzgerald, and Schnitzer 2013). Alternatively, neuronal activity can be measured by fractional fluorescence change $\Delta F/F$ used in fiber photometry, with careful consideration of indicator brightness, kinetics, and response characteristics.

The calcium indicator is widely used in optical imaging as neuronal activity induces calcium influx into the cytoplasm. Calcium responds to membrane events and generates a larger response through a prolonged biochemical process; however, its' slow kinetics makes the transient calcium peak 30 to 60 ms behind the actual spike (Helmchen, Borst, and Sakmann 1997, Chen et al. 2013). Calcium sensor GCaMP fuses calmodulin CaM and CaM-binding peptide to the N-terminal of cpGFP145 (Nakai, Ohkura, and Imoto 2001) and have been improved by many researchers. Currently, GCaMP6 series is widely used, with fluorescence change of 2,820%, and GCaMP6f can report a single spike with -20% $\Delta F/F$. GCaMP6s produces even larger response; however, it shows longer decays of 93%-190% (Chen et al. 2013, **Figure 6.2.3a**).

The fully trained animals were injected with GCaMP6s carrying the AAV virus, and then allowed for 7-14 days recovery (**Figure 6.2.3c**). Fiber photometry and data acquisition were done using a method described previously (Chuong et al. 2014, Kim et al. 2016a). Both a 405-nm LED and a 470-nm LED (M405F1 and M470F1, Thorlabs) were used as excitation sources either for Ca^{+2}-dependent or Ca^{+2}-independent isosbestic control measurements. The two light sources were filtered with either a bandpass of 410-10–nm or a bandpass of 470-10–nm (FB410-10 and FB470-10, Thorlabs). The emitted light then went into the microscope through a Φ 200 μm, 0.39 NA fiber and a 543 nm, f = 7.86 mm, 0.51 NA collimator (F240FC-A and AD12F, Thorlabs)(**Figure 6.2.3b**). As a consequence, the center part of the 400 μm patch cord was illuminated giving -254 μm diameter region. The LED light sources were combined with a 425-nm longpass dichroic mirror (DMLP425R, Thorlabs) and a 495-nm longpass dichroic mirror (FF495-Di02-25 $\times$36, Semrock). A custom wrote MATLAB software was used to control the sCMOS camera, the LED light sources were controlled by through a single chip computer (NI PCIe-6343-X, National Instruments), and data acquisition was performed with a custom wrote MATLAB script. The neuronal data, as well as AI-logs, were later used in the analysis pipeline in *R*.

6.2.6 Behavioral chambers and electronics

To control and acquire data from rat operant behavior, we used operant chambers, which were custom-made in-house. They were modified from existing chambers ((32 cm L $\times$ 25 cm W $\times$ 34 cm H, n = 4;

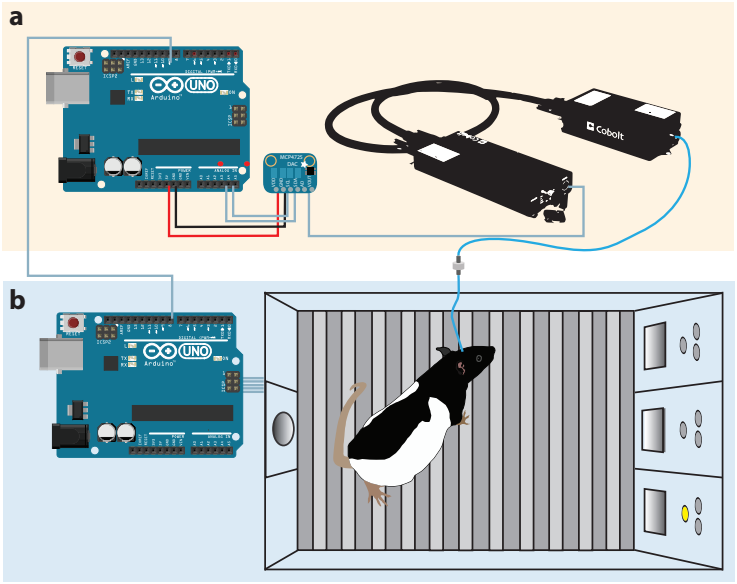

Figure 6.2.4: **a** Diode laser or DPSS laser were modulated by Arduino Uno32 as the photostimulation source. **b** Behavioral module consists of a custom-modified operant box with infrared sensors and LED stimuli source controlled by an Arduino Uno32 chip.

Med Associates Inc) with three custom-made nose-poke ports (6 cm L × 6 cm W × 16 cm H) on the front wall and one in the rear wall. All four ports hold three 5 mm LED lights (two white LED above one yellow 588 nm LED below), and the three front ports each held one liquid reward delivery sprout with a 5 volt DC pump. A 10 mm green LED (560 nm) was placed above the port on the rear wall as the house lamp (**Figure 6.2.4b**, **Figure 6.2.5c**). The lasers were also controlled by communication of the operant chamber controlling Arduino processor through a laser controlling module with predefined stimulation protocol (**Figure 6.2.4a**). All the nose-poke ports were equipped with two pairs of infrared sensors, consist of one 5 mm 940 nm LED light and one 5 mm 940 nm phototransistor (**Figure 6.2.5d**). The infrared beam breakers were used for registering nose-poke behaviors, and they were placed perpendicular to each other. Thus nose-poke artifacts generated by behaviors such as reward consumption could be removed. The operant chambers were wired to individual Arduino chips onto the pins as indicated by (**Figure 6.2.5a**); each pin can independently send or receive 3.3-volt digital signal. A custom-written Arduino script was designed as a finite state machine, tracking current behavioral states, all nose-poke events and the decision for state transition after a specific trigger. Therefore the operant chamber could be controlled automatically without human monitoring and can register time stamps and behavioral events.

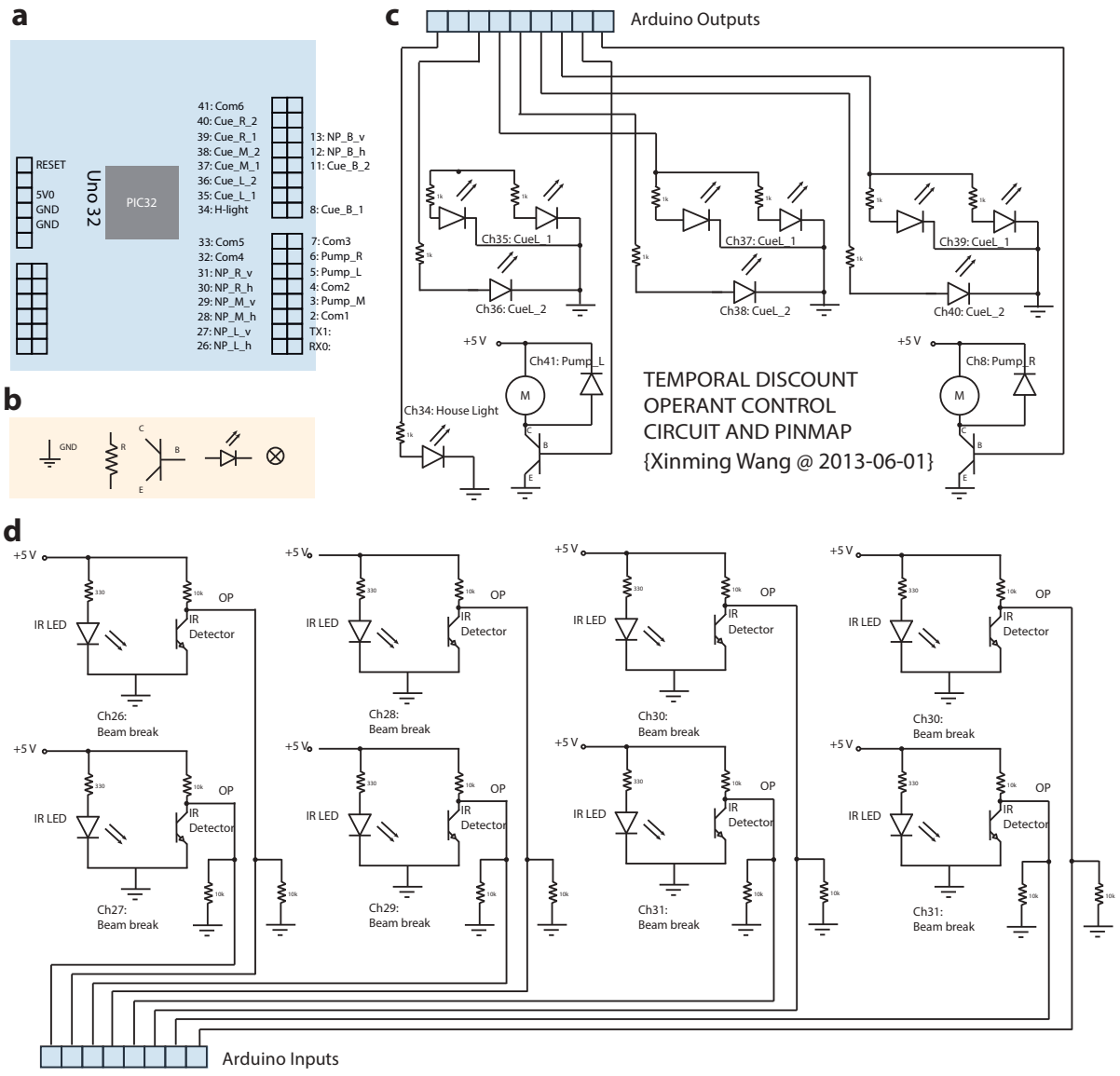

Figure 6.2.5: **a** Pin map on Arduino Uno32 chip. **b** Components lengend. c. Output channels and d. Input channels of the operant box.

6.2.7 Data analysis

The rat behavioral data was collected using a custom-written Arduino software, with time stamps and behavioral events recorded. All the data analysis was performed with *R* programming language (R Development Core Team 2015), and data visualization was performed with *ggplot2* (Wickham 2009). The exploratory analysis was performed to detect deviation from homoscedasticity or normality and outliers or the trials animals did engage (no nose-poke before the delay was elapsed). In the rat tasks, a nose-poke was defined as the simultaneous breaking of the horizontal and the vertical infrared beams in one port, and un-breaking of the beams was defined as the exit. All visualizations of the rat behaviors were normalized to the no-light condition for each animal, while the statistical calculations were performed on the raw data. Welch two sample t-test, and mixed effect ANOVA, were used to compare the nose-poke rate between the experimental group and the control group. In the time-discounting choice task, the binary target cue matching response was used as an outcome variable in a generalized linear mixed model (GLMM, Aarts et al. 2014) with a logistic link function using *lme4* package (Bates et al. 2015). The model parameters were estimated using Laplace approximation or Gauss-Hermite quadrature methods, and the Wald test was used for the significance test and was set to fulfill the maximal random effect structure. The final model was selected with the penalized likelihood method with Akaike information criterion (Vaida and Blanchard 2005). The peak time in the fixed interval task was estimated with the Gaussian function using the maximum likelihood method. $\Delta F/F$ in the fiber photometry was calculated using the normalized signal and median value in the signal channel previously described (Kim et al. 2016a).

"We know the past but cannot control it. We control the future but cannot know it."

Claude Shannon

7

Results, Conclusions and Discussion

7.1 Results & conclusions

7.1.1 Paper I: Prelimbic parvalbumin neurons control attention

Neuronal dynamic signature during top-down attention

In the 3-CSRTT, 13 PV-Cre mice were trained in the behavioral task. Chronic *in vivo* electrophysiological recording in mFPC resulted in 426 well-isolated single units as distinct neurons, from a total of 3,857 trials. These isolated units were later clustered into narrow-spiking or wide-spiking neurons based on their half-valley width, representing putative FS-PV neurons or putative pyramidal neurons, respectively. In addition, using an opto-tagging method in 4 PV-Cre mice, we were able to confirm that the 12 blue-light activated units showed the same electrophysiological properties of the narrow-spiking cells in chronically recorded animals. During the delay period in the 3-CSRTT, animals were required to be highly attentive and prepared to respond to a large spatial span with any potential stimulus. Premature response, omission, or incorrect nose-poke to the wrong port were scored as errors.

By examining the neuronal activities of FS-PV or WS neurons during the attention period, we identified

a steady increase of FS-PV activities in response to trial start, but the enhanced activities only sustained in correct trials. The significant increase of FS-PV activities started as soon as 300 ms after the trial initiation, therefore, activity of FS-PV cells was also a signature predicting success response 2.5 seconds before the cue onset ($p < 0.05$, paired t-test). In contrast, wide-spiking neurons were only slightly modulated during the attention period. An apparent dissociation of the wide-spiking population was found during the attention period, with 61% of the neurons increased activity while 39% of them were suppressed. Interestingly, the neurons with increased activity exhibited a lower firing rate in error trials, and the suppressed population showed a higher activity in error trials. The fastest and strongest inhibition of wide-spiking neurons was observed in correct trials and mediated by the FS-PV population.

Attentional processing

The response latency was measured as the interval between cue onset and the first nose-poke response. We found no correlation between response latency and FS-PV activity, neither between correct trials and different reaction time. It indicates mPFC FS-PV neurons do not encode task engagement nor motor preparation in general. When we only examined the trials with similar response latencies, FS-PV neuronal activity reflected the attention level, suggesting FS-PV does not play a role in response latency. In addition, reward latency that measures the interval between correct response and reward collection provided an index for animals' internal motivation status. We found no correlation between FS-PV activity and reward latency in the trials, arguing against the role of mPFC FS-PV neurons in encoding internal motivation states. Moreover, we were interested in the influence of choice history on current decisions. Our data illustrated that regardless of the previous choice, the degree of recruitment of mPFC FS-PV neurons was not affected, suggesting alternative mechanisms such as the timing of the recruitment.

Enhanced gamma frequency synchronization characterizes successful top-down attention

Local field potential analysis revealed that during the delay period, elevated 30–40 Hz gamma range activity was significantly associated with correct trials but not with the omitted trials. Analysis of incorrect trials also showed an intermediate increase of gamma power, suggesting animals were indeed engaged in the task. However, it was insufficient to perform the correct response. It is important to note that the elevated gamma was highly specific to the delay duration when attention was required. To investigate the mechanism of mPFC FS-PV neurons in the modulation of top-down attention, we analyzed the phase locking of FS-PV neuronal spikes two seconds before the delay was ended. The FS-PV neurons showed a high phase locking to the gamma cycle, with increased firing in the trough. The phase locking was strongest enhanced in correct trials, followed by suppression of local wide-spiking neuronal activities. Therefore, the firing rate of wide-spiking neurons was significantly regulated and phase locked to gamma range frequency. The phase-locking was either at the trough or the peak of each cycle only in the correct trials. Interestingly, two

distinct wide-spiking population were found that one group increased firing during attention while phase-locked to the trough of gamma, but the other group decreased firing during attention while phase-locked to the peak of gamma. Collectively, our data suggest that top-down attention was characterized by increased FS-PV activity and enhanced rhythmic temporal firing of wide-spiking neurons.

Causal function of mPFC FS-PV in top-down attention

We further tested the role of mPFC FS-PV neurons in the 3-CSRTT, which requires top-down control of attention and goal-directed actions. Inhibitory chloride-conducting channels (SwiChR, Berndt et al. 2014) were selectively expressed in the mPFC FS-PV neurons in 5 fully trained animals. The efficiency of light inhibition was verified in 4 PV-Cre mice with tetrode recordings. SwiChR was bilaterally expressed in the animals that were fully trained in 3-CSRTT. Brief pulses of blue lights (0, 1, or 2 seconds) were delivered to 50% of the trials (n = 4,362) pseudorandomly, and then terminated with a brief pulse of red light immediately after delay. Suppression of mPFC FS-PV neuronal activities during the top-down attention period caused a doubling of error amount with no correlation to duration of light inhibition ($p < 0.01$, paired t-test). More specifically, the errors were primarily due to increased omissions, suggesting inattentiveness in the task. It is importance to notice that neither response latency nor reward latency was affected by light inhibition of FS-PV neurons, indicating an intact function of locomotion and motivation status in the subjects with SwiChR inhibition.

Frequency modulation of top-down attention

Conversely, mPFC FS-PV neurons can be selectively activated by ChR2 so that we could investigate the functional impacts of artificially generated synchrony in the local circuitry. In 5 fully trained animals, ChR2 was bilaterally expressed in the mPFC FS-PV neurons. Brief blue light pulses were applied pseudorandomly for two seconds before reward delivery in 50% of the trials (n = 10,302). Activation of mPFC FS-PV neurons at the lower frequency (1-10 Hz) surprisingly increased premature response and omission significantly ($p < 0.01$ paired t-test), where premature response reflects impaired function in impulsive control. Activation of FS-PV neurons at gamma frequency (30–40 Hz) indeed significantly decreased the number of omitted trials ($p = 0.01$, paired t-test) demonstrated an instant and short lasting pro-cognitive effect due to artificially induced of gamma synchrony. No significant change of behaviors was observed by activating mPFC FS-PV neurons in other frequency ranges. Furthermore, we notice that neither response latency nor reward latency was affected by light inhibition of FS-PV neurons, indicating an intact function of locomotion and motivation status in the subjects with ChR2 activation.

7.1.2 Paper II: NMDAR deficiency in parvalbumin neurons

NMDA-dependent activity of FS-PV neurons in depressive-like behavior

We established and applied a repeated forced swimming test, which enabled the examination of the sustained effect of antidepressants over a long period. The animals (NR1f/f, n = 10; PV-Cre NR1f/f, n = 10) were injected with saline (i.p.) 30 min before the first exposure of FST. Then the test was repeated 24, 48, 72, 96 and 240 hours after saline injection. The test showed a low variation of immobility within each group, indicating a high reliability of the test. We could not find any significant difference in immobility between the two tested groups ($p > 0.05$ one-way ANOVA), contradicting the hypothesis that NMDAR in FS-PV neurons was necessary for expression of depressive-like behaviors. We further explored the antidepressant effects of non-selective NMDAR antagonist ketamine and selective NMDAR antagonist MK801. We examined immobility and swimming activities in animals with or without NMDAR in FS-PV neurons. The confounding effects on locomotion of ketamine (3 mg/kg) or MK801 (0.1 mg/kg) were controlled by i.p. injecting the drugs or saline, and thereafter measured in open field test.

Both single dose of ketamine (3 mg/kg), or single dose of MK801 (0.1 mg/kg) significantly rescued the expression depressive-like behavior, exhibiting instant lowering of immobility and increase of swimming. More specifically, one acute dose of ketamine reduced 40% immobility ($p < 0.001$, two sample t-test) 156% increase of increased swimming ($p < 0.001$, two sample t-test) whereas MK801 reduced immobility by 22% ($p < 0.05$, two sample t-test) and increased swimming by 240% ($p < 0.05$, two sample t-test) 30 min after injection. Long-term effects after 24 hours or 1 week were also examined, only ketamine showed a persistent effect after 24 hours (24% less immobility, 106% more swimming, $p < 0.05$ Student's t-test). Animals with or without NMDAR in FS-PV cells, surprisingly, showed no significant difference in immobility ($p < 0.05$ two sample t-test) in response to either ketamine or MK801

Anhedonia is not dependent on NMDAR in FS-PV neurons

A sucrose preference test was used to further examine the anhedonia related symptoms such as declined experience of pleasure. As treatment of NMDAR antagonists reduces anhedonic behaviors, we also tested if NMDAR in FS-PV neuron potentially played a role in motivation or reward processing. Animals with or without NMDAR were placed in the test chamber, where they could freely choose sucrose water or plain water for 72 hours. Our results revealed no difference in sucrose water intake between the animals with (1.67 ± 0.10 grams) and without ($1.87 \pm .10$ grams)($p > 0.05$ two sample t-test).

7.1.3 Paper III: Dorsal Raphe serotonergic neurons control impulsive behaviors

Genetic targeting of DRN 5-HT neurons

To enable genetic targeting and *in vivo* optogenetic control of DRN 5-HT neurons for later examination of the role of DRN 5-HT neurons in impulsive behaviors, we generated transgenic recombinase-driver rat lines using a rat *tph2* gene containing bacterial artificial chromosome (BAC). The Cre gene was inserted right after the ATG codon in the BAC construct, and the efficiency and specificity of the construct were validated using DIO-AAVs carrying fluorescence-coupled opsins. We analyzed offspring rats from the top two ranked founder lines with efficient and specific recombination. Specifically, in line 1, 99±1 % of the fluorescence expressing neurons in DRN expressed 5-HT (n = 305, N = 2), and in line 6, 100±0 % of the fluorescence expressing neurons in DRN expressed 5-HT (n = 280, N = 2). Offspring from both lines were used in the current study. The electrophysiological functions induced by light activation or inhibition of ChR2 or Jaws were further tested with *in vitro* whole-cell recording. All neurons expressed ChR2 (n = 13) increased firing rate with either 20 Hz (paired t-test, $p < 0.05$) or 60 Hz (paired t-test, $p < 0.05$) blue light stimulation. And all Jaws expressing neurons (n = 9) exhibited strong amber light-evoked inhibition of current induced spikes.

DRN 5-HT neurons regulate impulsive action

In the fixed interval task, animals were fully trained to associate three distinct visual stimuli to three fixed intervals (8, 16, 32 seconds delay, one port for each). The response rate (NPR) during the delays was measured as an index of impulsive action. Animal only could receive the reward (200 μl 10% sucrose in water) only after the fixed delay had elapsed. Thus, the NPR formed a peak at the end of distinct fixed delays and showed scalar effects over delays (Pearson's r = -0.9991). Using optogenetics, with light stimulation between trial initiation and reward delivery, we found NPR during 5 seconds before or after fixed delays were significantly higher with Jaws inhibition (% change in relation to control, 5 second before fixed delays: 8 seconds delay: 27.67 ± 10.46 %, $p < 0.05$; 16 seconds delay: 86.98 ± 11.07 %, $p < 0.001$; 32 seconds delay: 39.07 ± 9.43 %, $p < 0.05$. 5 second after fixed delays: 8 seconds delay: 49.23 ± 6.85 %, $p < 0.001$; 16 seconds delay: 67.55 ± 8.36 %, $p < 0.001$; 32 seconds delay: 37.12 ± 8.58 %, $p < 0.01$, mean ± SEM, n = 3838, N = 7). Conversely, increased activity of DRN 5-HT neurons showed a trend of decreasing impulsive action, however with much smaller effects. The largest and msot significant effect was seen with 60 Hz drive in trials with the longest delay (5 second before fixed delays, 32 seconds delay: 23.13 ± 7.01 %, $p < 0.05$; 5 second after fixed delays, 32 seconds delay: 21.13 ± 5.84 %, $p < 0.05$, mean ± S.E.M.). The same modulation of impulsive actions were also observed in the probe trials, which randomly appeared at 25% chance, with 3 times delay duration, but no reward delivery. No significant main effect on the mean NPR of *Light* can be identified by its own ($F_{(1, 5)} = 3.53$, $p > 0.05$, mixed effect ANOVA), demonstrating that application of light without opsin cannot modulate impulsive action, but significant *Light* × *Opsin* interaction ($F_{(3, 5)} = 3.53$, $p < 0.01$, mixed effect ANOVA) confirmed the role of DRN 5-HT neurons in impulsive action.

DRN 5-HT neurons do not modulate subjective timing

DRN neurons have been shown to be involved in timing from several studies with mixed results. In the fixed interval task, we compared the time point for the first and last nose-poke response during the delay (i.e. the Start Time and Stop Time, respectively) in unrewarded probe trials with and without light manipulation. Our data illustrated that changing the level of DRN 5-HT activity did not alter the timing of the first nose-poke response (*Light* × *Opsin* interaction effect: $F_{(3,45)} = 0.179$, $p = 0.91$, mixed effect ANOVA) nor the timing of the last nose-poke during the delay (*Light* × *Opsin* interaction effect: $F_{(3,45)} = 0.097$, $p = 0.96$, mixed effect ANOVA). The peak time fitted with Gaussian distribution showed no effect on the Peak Time with optogenetics (*Light* × *Opsin* interaction effect: $F_{(3,44)} = 2.31$, $p = 0.089$, mixed effect ANOVA). Taken together, our 'ultra-acute' optogenetic modulations directly argue against a regulatory role of DRN 5-HT neurons in subjective time perception.

DRN 5-HT neurons encode reward

In the fixed interval task, we recorded *in vivo* Ca^{2+} activity change selectively in DRN 5-HT neurons in fully trained animals. The calcium indicator GCaMP6s was injected in fully trained animals, followed by fiber optic implantation. The neurons showed elevated activity during waiting period and robust responses upon reward consumption, in six consecutive recording days (n = 478 trials, N = 5). All animals displayed a similar and specific modulation of Ca^{2+} activity during distinct fixed delays. We also compared 5-HT population activity between the five last seconds before the rewarded nose-poke and during reward consumption. ($\Delta F/F$ compared between 0-2 seconds after trial initiation and -5 to 0 seconds before reward delivery; 8 seconds delay: $p < 0.05$; 16 seconds delay: $p < 0.05$; 32 seconds delay: $p < 0.01$, paired t-test).

DRN 5-HT neurons directly control impulsive choice

In the time-discounting choice task, fully trained animals were required to only respond to the visual cues that matched the target cue presented in the central port in the operant chamber (n = 14,969 trials). Two types of cues signaled smaller sooner (SS) or larger longer (LL) reward. We used optogenetics to directly modulate the DRN 5-HT neuronal activities in behaving animals expressing light-sensitive opsins, ChR2 (n = 3), Jaws (n = 3), or eYFP (n = 2). Our results illustrated that the willingness to wait for an LL reward was inversely related to the delay duration ($p < 0.01$, Wald test) as commonly observed. Optogenetic activation significantly increased the willingness measured by response accuracy to wait for LL rewards ($\beta = 0.38$, $SE(\beta) = 0.13$, $z = 2.94$, $p < 0.01$, Wald test, GLMM). Conversely, the inhibition of DRN 5-HT neuron activity resulted in lowered patience to wait for LL rewards ($\beta = -0.41$, $SE(\beta) = 0.12$, $z = -3.39$, $p < 0.01$, GLMM). However, no effect was observed in the control animals with eYFP and light stimulation ($p > 0.01$). We also could not identify any significant fixed effect from *Light* alone ($z = 1.09$, $p > 0.01$). Further analysis showed that increased impulsive choice by suppressed DRN 5-HT neuronal activities was also

accompanied by increased impulsive action in the time-discounting choice task. By examining the NPR in the LL trials when animals made responded correctly, our data demonstrated a significantly higher NPR with Jaw inhibition, although the animals were less willing to wait for LL rewards ($p < 0.01$, two sample t-test).

7.2 Discussion

7.2.1 Implications in practice

The studies in this thesis provide new insights into our understanding of the neuroscience of decision-making, particularly, in Paper I, regarding the mechanisms of goal-directed top-down attention regulated by FS-PV neurons in the mPFC. The neuronal activities of mPFC FS-PV cells predict successful allocation of attention and behavioral outcome in mice. Such regulation is characterized by frequency-specific modulation of principal neurons through a phase-locking mechanism. The manipulation of mPFC FS-PV neuronal activities directly changes the performance in the top-down attention task. Moreover, in Paper II, our results invalidate the hypothesis that NMDAR in FS-PV neurons plays a key role in the expression of depressive-like behaviors. Furthermore, in Paper III, using optogenetics and optical calcium imaging, we show that long-range ascending projections from DRN 5-HT neurons encode reward and delay in impulsive behaviors, manipulation of the neuronal activities in DRN 5-HT population directly regulates the expression of impulsive behaviors including impulsive action and impulsive choice.

Dysfunction of decision-making is one of the symptoms of mental disorders. Various forms of decision-making dysfunction are highly disabling for individuals and cast a significant economic burden on the society. The cost is estimated to be more than $15 trillion in total during the next 20 years, not to mention the potential costs from suboptimal decisions individuals, organizations, or the government may make. Many decisions will have long-lasting effects on our welfare, the society, environment, and the future generations. Studies of the neuroscience behind decision-making have already made some great impacts on individuals with obstacles making their choices and also assisted organizations to make better decisions. For instance, studying the rodent brain, which is hundreds of times smaller than the human brain, sheds light on understanding the maladaptive reward status in the human brain. Studying the reward-seeking behavior with fMRI in awake rodents revealed causal evidence for behavioral significant brain regions (Ferenczi et al. 2016). Those regions are highly conservative between the rodent and the human. The rodent PrL cortex is functionally homologous to the human dlPFC, and rTMS targeting the human dlPFC can produce similar behavioral outcomes as suppression of the rodent PrL cortex.

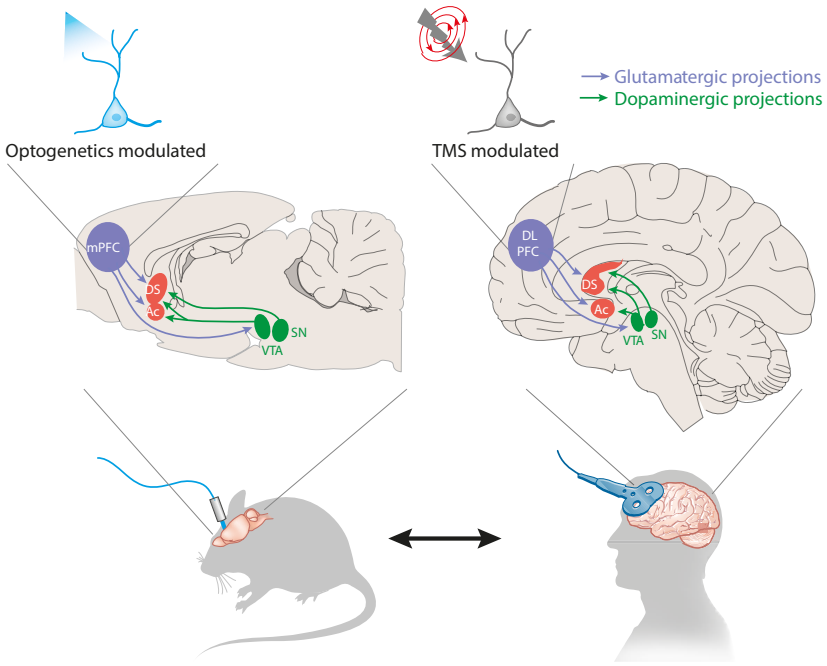

Figure 7.2.1: **a** Optogenetic dissection of the functions generated from genetically coded circuits. **b** The identified potential target can be translated to human medical treatment as the brain structures are highly conservative during evolution. (Modified from Ferenczi and Deisseroth 2016 with permission)

With the powerful knowledge of evolutionary conservation in the brain function across species, one can translate and validate behavioral modification methods in humans. Individuals with cocaine-addiction were treated using rTMS targeting their dlPFC with brief pulses for 13 minutes, five times during the first week and one time during the following three weeks (Terraneo et al. 2016). The rTMS-treated group showed more than three times of chance being drug-free (drug-free chance: rTMS: 69%, cocktail treatment: 19%) in the initial phase, as compared to the control group with traditional pharmacological cocktail therapy, and no relapse before day 12, whereas 50% of individuals relapsed in the cocktail group. In the long run, only three out of ten were tested cocaine positive. This result illustrates one basic neuroscience-inspired application for improving human cognitive dysfunction. It was a direct translation from the insight of the rodent PrL role in reward-seeking behavior and top-down control to the human dlPFC-related mental disorder. The exact mechanisms of such regulation are nowadays often revealed with optogenetics and other methods with gain or loss-of-function, which made a substantial transformation in the real-world applications. The same principle can be applied to Parkinson's disease using deep brain stimulation (Gradinaru et al. 2009) or in another choice for disabling phenotypes, such as anxiety or depressive symptoms in psychiatric disorders (Deisseroth 2014).

7.2.2 What's next?

It is encouraging that findings in basic neuroscience can already make a great impact on individuals, as well as improve people's decision-making and life quality. There still exist many questions before we can precisely locate the brain circuit for the efficient treatment of a symptom. For example, knowing the interneurons are embedded in an intricate and interconnected network, what's the best way to single out their function? Is it even logical and possible to single out their functions? Is there any other way of finding out the answer? One of the keys is to understand how the brain performs the neuronal computation. It will be immensely challenging to understand the fundamental principles of decision-making without it. Luckily, with the advancements in technology, such as *in vivo* neural imaging, optogenetics, and circuit connectomics, we have acquired and accumulated a substantial amount of knowledge about neuronal activities and related decision-making processes. Both the scope and the depth of our understanding of the brain are expanding in an accelerated way (Hamel et al. 2015). *C. elegans* is one of the model organisms with all the neuronal circuitry mapped out with all the biochemical and electrophysiological information (White et al. 1986, Jarrell et al. 2012). Using genetic viral tools, such as monosynaptic retrograde virus, a part or a subsection of a circuit in the brain (Watabe-Uchida et al. 2012, Pollak Dorocic et al. 2014) or complete map in a simpler structure like the retina (Helmstaedter et al. 2013) can be revealed in rodents. Moreover, it is now possible to image all the connections in a rodent brain, as well as render and visualize in a three-dimensional space (Oh et al. 2014, Chung and Deisseroth 2013).

Pioneers, such as the Allen Institute for Brain Science, made a great effort in gathering information with standard procedures. The effort was later joined by several national and international projects such as HBP in Europe, BRAIN initiative in the U.S., MIND in Japan, and China Brain Project, aiming to decipher the brain's functions. However, a significant amount of information or knowledge is useless unless we turn them into insights, and unfortunately, there isn't a simple way. A vast amount of new knowledge is accompanied with high complexity and enormous size of the data. Also, there is no simple way of sharing data as the application programming interface does in computer science. Gomez-Marin et al. mapped the behavioral problems onto a 3-dimensional space with axes "Degree of constraints", "Dimensionality of metric", and "Level of description" (Gomez-Marin et al. 2014, **Figure 7.2.2**). Using those three axes, all decision-making paradigms can be mapped into that space. For example, head-fixed behaviors or 2-alternative forced choice are constrained by control and fixation of many variables but generate reasonable levels of description and conclusion about some aspects of real world problems. On the contrary, field studied with a high-speed camera can give high data dimensionality, but do not necessarily describe a single decision problem precisely.

To take advantage of new technologies and push our understanding of decisions forward, neuroscientists need to make use of methods and tools from other fields. Historically, the invention of computers and the later explosion of computing power takes our research in neuroscience great leaps forward. Our understanding of the brain and decision-making process was elevated from descriptive microscopic examinations or behavior observations to general elementary insights and theories. Nowadays, computer scientists are using artificial neural networks to solve problems that were previously believed unconquerable (Silver et al. 2016) from natural language processing (Hermann et al. 2015) to reinforcement learning for visuomotor training (Levine et al. 2015) or computer vision for image segmentation and recognition (Szegedy et al. 2016). But how? Mathematicians constantly improve their toolkit with more powerful statistical techniques and models, and neuroscientists mapped out the basic structure of visual information encoding and processing (Moreno-Bote et al. 2014). Therefore, a human visual system mimicking convolutional neural network can be used to serve the same purpose as computers to recognize images. Similarly, dimension reduction was no new problem, as the brain has done this job daily for millions of years, and brain-inspired artificial neural networks simply would do the same job (Hinton and Salakhutdinov 2006).

The brain-inspired artificial neural network is one of the most exciting research fields, and it generates numerous of applications for the real-world decision-making problems, such as in medicine and many other sciences and industries. Diagnosis of cancer largely relied on pathological examination of biopsies from the patients, and human experts would give a conclusion based on previous experiences, available information, etc. One of the major challenges for the human experts was the variability in morphology and appearance of cancer tissue. Esteva and colleagues trained a neural network with more than a hundred thousand images; remarkably, the trained network can reliably identify skin cancers from the images, with a comparable accuracy to dermatologists (Esteva et al. 2017). In a more complex situation, where not only simple decisions such as classification is required, but also require global consideration of the collateral or long-term impacts, adding a separate neural network for policy revolutionized the classical game Go (Silver et al. 2016). With two networks trained, no human master could reliably defeat the artificial neural network.

The brain is way more advanced than any of the artificial neural networks both in structure and computational performance. Although it can not process millions of numeric computation simultaneously and the speed of the neural signal is much slower than the current flow in a computer chip, the brain adaptively handles different tasks and make decisions accordingly with general intelligence, which is still impossible to achieve in any silicon-based system. Birds' wings inspired us, then we developed machines for flying; bats' ears inspired us, then we developed devices for detecting objects. Now, the era has arrived when the brain-inspired tools will assist us to generate smarter solutions, enable us to tackle a broader range of issues, and reduce the cost because of limitations in decision-making. In Sweden, inaccurate predictions of wind speed

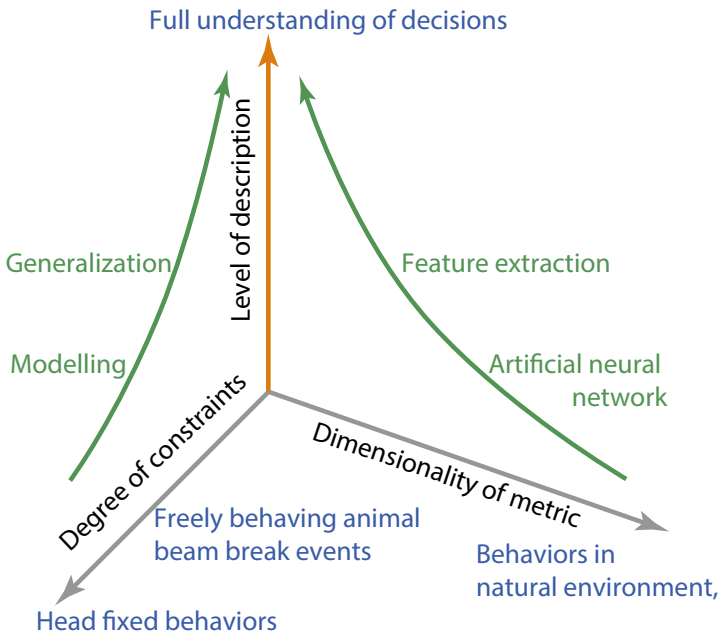

Figure 7.2.2: Different behavioral assays for the understanding decision can be mapped onto a three-dimension space including the degree of constrains, dimension of metrics and level of description. While classical experiments used high constraints, new technologies increase the metric dimension and reduce the cost. Thus the knowledge can move in this 3-D space towards higher description. (Inspired and modified by Gomez-Marin et al. 2014 with permission)

cause a tremendous loss of money for the electricity grid operators who need to switch between hydro- and wind-power holding wrong information. With the help of a neural network-driven deep weather project, it takes the old work performed by a super computer to a laptop, saving a considerable amount of monetary and environmental cost.

7.2.3 Honestly, how well do we understand the brain?

Advances in artificial neural networks are fast and exciting. However, it treats the brain mostly like a black box, and no more than a handful of scientists know what's going on. Is it going to be a problem? Imagine a scenario in which we don't know the basic principle, such as how computers create, store, and retrieve variables. One group of researchers sets out to investigate the input-output function of a bigger network - the Internet. They can treat it as a black box and record all the events. One of the interesting signatures related to this could be an increase in travel destination searches in a specific part of the Internet, say Sweden, during March and August. After careful repeating of the observations over the years, they conclude Sweden, in the whole Internet 'encodes', traveling. To confirm a causal relationship, they can give a 'stimulation' only in Sweden, with promotions and campaigns, and it's likely they will find an increased Internet activity response to the 'stimuli'. In the end, we can pin functions to specific 'regions' from a bigger network during a particular period, but we still don't know how a travel destination is coded in the network. One can even

reconstruct the input-output relationship with an artificial neural network and likely get a replica of such behavior, but no one knows how and why it will work.

This is, however, an extreme, hypothetical scenario, which might not even be remotely related to how research is done in neuroscience. The point is although we gathered a rich collection of insights into how the brain functions, there is one important piece missing. The problem is on the other side of the real-world application, that is, the simple principle of neural coding. Examples like the one previously described illustrate that we lack this simple principle that depicts the fundamental problem. The key to the Internet example is to know that any form of data is stored in bits of zeros and ones. They're physically stored in each node, i.e., local machines' memory or hard drive. Each piece of information has a distinct address bus and a common data bus, which form the basic information storage structure. More importantly, such structure is the universal basis for retrieving and decoding any information we send through the Internet. In neuroscience, we somehow lack the understanding of the fundamental principle of the coding and decoding of information (**Figure 7.2.3c**). Although we have all the data and insights around the core problem, we just don't know how the core functions. This situation will be comparable to research in genetics, knowing all the molecular machinery about their composition, binding, dynamics, etc., but not knowing the triplet code nor the central dogma (**Figure 7.2.3d**).

There are several papers that raised concern about the associative methodology in biology (Lazebnik 2002) or neuroscience (Jonas and Kording 2017) using the known systems of electronic engineering. Although the scope of this thesis is very different from those studies, the concern is still valid. The brain has billions of neurons and quadrillions of connections, so it has been admittedly difficult to decode the communication between source and receiver. Here source and receiver can be a sensory stimulus, a cone cell in the retina, a hippocampal pyramidal neuron, or any parts where information needs to flow through. The herculean challenge is: when we intercept their communication using electrophysiological or optical recordings, how do we get a meaningful message out of it? There are so many studies that reported neurons encode various events, choices, and emotions, but no study reported a successful decode of a neuronal message that encodes the event (**Figure 7.2.3c**). The same challenge dated back almost 80 years, when British intelligence attempted to decrypt the German Enigma machine, which had 186 million million million configurations (**Figure 7.2.3a**). They learned that the device could take an input, which is a key press, then current flows through several mechanical wheels scrambled, and generate an output letter after each input (**Figure 7.2.3b**). Therefore, even if the researcher physically possessed the machine, it was impossible to decipher one message. A similar situation is that we're strangled by an astronomical number of variations among brains, and connections within one brain, even if we can get a good number of messages out from the brain. (You can test the input-output system here `http://enigma.louisedade.co.uk/enigma.`

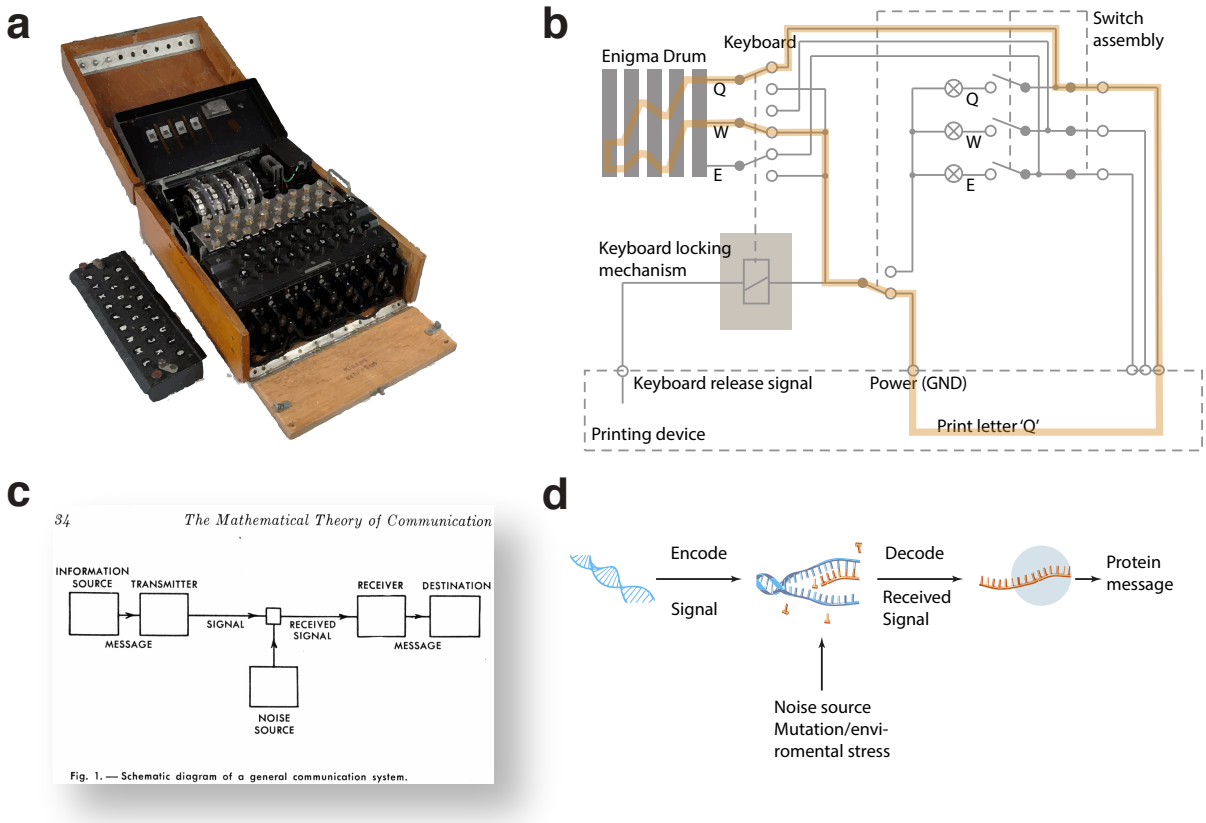

Figure 7.2.3: **a** Enigma machine used for German army during World War II. **b** Illustration of the circuit diagram of the machine. **c** The principle of communication. **d** An example of a real biological encoding/decoding system.

html)

One can record input and output from the brain or the enigma machine simultaneously in as many trials as possible with the machine, then perform advanced analytics. But the cryptanalyst had already realized that the enigma machine was immune to frequency analysis. The machine could encode all possible information that a sender intended, as the brain can encode an infinite quantity of information, as far as our imagination can reach. That includes information about the weather, military orders, family talks, etc. The talented team, including Allan Turing, noticed there were non-coding sequences 'call signs' at the start of all the cipher text, as the address of the message. The cryptanalyst then started 'traffic analysis' by building a German communication network among nodes, and established edges that illustrated the communication network. One good thing which came out of a large number of trials was that they spotted a flaw. That

flaw was that the machine would never change one letter to itself, which eliminated many combinations between the text and cipher text. Using *cribs* in which a ciphertext often reappeared with a message number, for the weather report, the British intelligence scientists used the Bombe machine to eliminate wrong configurations. The process was also limited to each day because a configuration would start the next morning. Without *cribs*, it could take a modern computer one month to decipher the text on a piece of paper given that one knows how.

Coming back to the original problem, we are trying to find the method of information encoding and the location of information storage in the brain. A connectionist would suggest the synaptic plasticity model, as one has learned from the psychologists that the brain learns from association. However, in such models, no one has provided information, such as the smell of food, the color of a book, the President of the U.S., etc. are encoded. We have accumulated a fair amount of knowledge in understanding the decision-making mechanism or, more generally, the brain's code. We know already that one brain region can perform various of tasks. We also know that only one neural circuit can perform a complex task, such as drive reward-seeking behavior or do classification of tumors. Therefore, it is no surprise that we find one cortical area coding all information in decision-making, such as in OFC (Stalnaker, Cooch, and Schoenbaum 2015). As discussed in Chapter 2, one should not fall into the trap that assuming more information translates to a deeper understanding, particularly for the scientists. One should carefully examine all associations and evidence that we have at hand, devise testable theories or hypotheses and, most importantly, identify the wrong alternatives, and share the negative results among the community, so we can crack the brain's code, just as what Turing did to break the Enigma. Luckily, we have now constructed a 'traffic' network in the brain indicating the hubs where information flows through, and a tiny step forward would be to find the *cribs* of the brain?

ACKNOWLEDGEMENTS

The work included in this thesis would never be accomplished without the help of many of my colleagues, friends, and family. I would like to express my deepest gratitude to everyone supporting this research and my life.

First of all, I would like to thank you Marie Carlén for introducing me into the field of system neuroscience, for taking me into an amazing lab so I can grow with talented colleagues here. I appreciate the atmosphere of freedom in research, so I developed necessary skills to be an independent scientist. I also would like to thank you Dinos Meletis, for never ceasing thought trains of ideas, for all your help making the transgenic animals to succeed, and for your endeavors of making all the social and fun event in the lab. I would like to thank you Per Svenningsson, for all your supports and insightful discussions. I would like to thank you Staffan Cullheim for being very helpful and encouraging in my work and life.

I also like to thank the wonderful crew from the DMC lab, Hoseok Kim, Daniel Fürth, Ourania Tzortzi, Yang Xuan, Josina van Lunteren, Naz Karadag, Mikael Corell, Nicolas Gustavo Guyon, Sofie Ährlund-Richter, Iakovos Lazaridis, Moritz Weglage, Antje Märtin, Laura Pozzi, Chase Clark, and Cantin Ortiz. Thank you for all your support and input into the project, I feel very fortunate to have such a journey with you. You make the lab filled with enjoyment and inspirations, and I enjoyed every moment with you guys. Special thanks to Hoseok for teaching and helping me with electrophysiology and data analysis; Daniel for spending many evening together in insightful discussions, and all your help in my questions from statistics to psychology; Rania and Antje for the love and care you brought to the lab; Yang for your patience and chat in Chinese; Nicolas for your discussion in world politics and your black jokes; Sofie for driving the fun and making all the party happens; Iakovos, Laura and Mikael for taking care of the lab and everyone else very nicely.

I would like to thank all my colleagues in the department, Jianren Song, Yu Qian, Kai Du, Joanne Bakker, Mingdong Zhang, Swapnali Barde, Yiqiao Wang, Haohao Wu, Yongtao Xue-Fransén, Carolina Bengtsson Gonzales, Jakub Lewicki, Xiaofei Li, Débora Masini, Maya Ketzef, Matthijs Dorst, Yvonne Johansson, Tim Arentsen, Stephanos Stagourakis. It was such a pleasure to work at the same place with you guys. Thank you for the lunch chat on various of topics with Song, Sam, Kai; Maya, Yvonne, Joanne, Caro for all the fun parties and lots of drinking; Xiaofei and Kuba for being hilarious and make your corridor filled with stories; and Débora for your caring and support.

Many thanks to Gilad Silberberg, Abdel El Manira, Gilberto Fisone for those fruitful discussions with you, valuable suggestions, and being supportive and encouraging. I would also thank my mentor Michael Ändang for engaging me in my first research project here and suggestions about life.

I also want to express my thanks to my friends I met at Karolinska: Giulia Gaudenzi, Mustafa Ismail, Maria Papathanou, Joana Flores, Su Bächle, Khayrun Nahar, Espen Hesselberg, Mario Hermann, Cécile Zaouter, Sohye Yunn, Ana Rosa, Anwarul Quadir, Erik Müller, Elin Helander. My special thank to Giulia for being the trust one I can always turn to; Sohye and Ana for a great adventure we took and amazing trip in Lisbon; Erik for being inspiring and life advice; Elin for all the lively discussions and fun projects in behavioral economics.

Many thanks to my friends here in Sweden: Yuning Zhang, Menghan Gao, Yixin Wang Jiaqi Huang, Ci Song, Zheng Chang, Xi Liu, Heng Wang, Tong Gong, Ran Ma, Yao Shi, Rui Wang, Tong Liu, Huiyuan Zheng, Xiaobing He, Jian Zhao, Na Guan, Ning Wang, Juan Du, Bin Zhao, Wei Jiao, Zhuo-Chun Peng, Qiang Zhang, Meiqiongzi Zhang, Lidi Xu, Meng Chen, Andrew Wu, Ying Qu, Chang Liu, Xiao Tang, Jiangrong Wang, Xiaoyuan Ren, Chen Suo, Qin Xiao, Dong Yang, Julie Qiuling Huang, Zhili Song, Huan Song, Jianwei Zhu, Daohua Lou, Junwei Zhang, Yunlong Yang, Ying Ye, Yingbo Lin, Qinzi Yan, Shuo Liu, Shanshan Xie, Dan Dou, Jan Hsia, Tal Gilad, Annika Hirvonen Falk, Zi Ning, Chengkai Yang, Yan Dou. It is because of having you around, I have a wonderful and warm feeling that Stockholm is my second hometown.

All my former colleagues from the lab and the department, Zia Uddin Darokhan, Artak hachatryan, Victor Salander, Calvin Young, Cleiton Lopes Aguiar, Åsa Konradsson Geuken, Daniel Kaping, Charlotte Alme, Niten Olofson, Hester Meeusen, Marc Parent, Iskra Pollak Dorocic, Solmaz Yazdani, Lovisa Fransén, Jo Clerke, Ed Li, Felix Wahl, Aileen Gracias, Michael Feyder, Lovisa Case, Li-ju Hsu, Esra Karaca, Michalina Lewicka, Caitlin DuPont, Susanne Szydlowski, April Johnston, Ramón Reig, Ming Zhou, Richard Andersson, Sophia Savage, I would like to thank you for making my journey very special and filled with cherished memories. My special thank to Calvin for bringing many knowledge to me and in-depth discussion in science; Daniel for the wonderful years and hours we spent together and make our ideas came true, and also many things I learned from you; Hester for your great help in the study and being an awesome

student; Marc for the discussion and passion in data science; Iskra for being the longest and developed together in the lab, also bringing all the debates between Canadian and Swedish system; Esra, Michalina and Aileen for being inclusive to the young DMC crews and nice parties; Ming for your dedication to the project and friend.

Thanks to my lifelong friends: Iolanthe Lan, Jingshu Zhang, Rong Su, Yanyu Zhang, Miao Teng, Ying Hu, Jing Han, Lingxuan Liu, Estelle Zhao, Hao Hao, Yuqing Dong for always reachable and providing me a feeling of comfort and happiness.

I would also like to thank Ulla Haglund for being like the mother to me. You taught me so much about Swedish society, culture, and food. Thank you for taking me to see and learn this fantastic country, and having me over for the most beautiful summers in Dalarna. Thank you, Qiaolin Deng, Zhe Jin for always receives my family to your house with open arms, so we don't feel alone but taken in.

To my dearest parents and my extended family, thanks for your enormous love and support.

致我最亲爱的父母，是你们不倦的教诲才让我取得今天的成绩和生活。妈妈，你的善良，你的无私奉献以及生活的智慧时时不在让我成长。爸爸,你的严厉和认真一直是激励我追求更好的榜样和动力。十年求学在外，多少无言的期许与帮助。现在儿子也已经成为父亲，深知你们不图回报，只希望你们健康快乐。

Last but not the least, I would like to express my deepest gratitude to my wife Celine Xu and my son Ethan Jinghan Wang. Thank you, Celine for supporting all my decisions, for making my life so colorful, for the same goal we fight together. Thank you Ethan for transformed my life and my view of life, and you made me realized what matters in my life.

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