Title: Dopaminergic Mechanisms Underlying Human Social Behavior

NCT Number: NCT04205994

Protocol Approve Date: 11/2/2021

CONSENT TO PARTICIPATE IN RESEARCH
Dopaminergic Mechanisms Underlying Decision Making

Key Information

- You are being invited to participate in a research study. Participation in research is completely voluntary.
- The purpose of the study is to understand how the level of a brain chemical called dopamine can affect decision making.
- The study will take a total of 13 hours spread over 3 visits. You will be asked to make decisions while you are in the MRI scanner after you have taken either a medication (tolcapone) or a placebo (a pill that has an inactive substance in it).
- Risks and/or discomforts may include fatigue or frustration related to behavioral testing; discomfort related to MRI scans; rarely lightheadedness, anxiety, or other side effects related to tolcapone; and possible future risk of the genetic tests linking genes to a clinical condition, resulting in psychological or social risks if the information is unexpected or unwanted, or the knowledge might alter reproductive decisions, employability, or insurability.
- There is no direct benefit to you. The results from the study may someday help us to better understand and treat disorders of decision making.
- Taking part in this study is your choice. Your alternative is not to take part.

Introduction

My name is Ming Hsu, Ph.D. and my research colleague is Andrew Kayser, M.D., Ph.D. I am a faculty member, and Dr. Kayser is a research scientist, at the University of California, Berkeley in the Helen Wills Neuroscience Institute. We are conducting a medical research study, which we invite you to take part in.

You are being invited to participate in this study because you are between the ages of 18-40 years old and you are otherwise healthy.

Purpose

The purpose of this study is to investigate how people make decisions about rewards. We want to understand how the brain's dopamine system impacts this kind of decision-making. We will use a medication called tolcapone that can temporarily affect the dopamine system. We also want to know if genetics or personality traits change how this drug affects decision making. About 200 people will take part in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Procedures
If you agree to be in this study, you will be asked to do the following:
You will undergo a screening visit either in person, or remotely via video (or, if video is not possible for you, telephone) at a time that is convenient for you. If you qualify you will then be invited to the U.C. Berkeley Imaging Center (BIC) or the U.C. San Francisco research clinic, whichever is more convenient for you, for 2 more visits. These visits will be scheduled when it is convenient for you. Within approximately 6 weeks of your screening visit, you will return for the first of two MRI visits. The second of the two MRI visits will usually be completed within about 3 weeks of the first MRI visit. However, it could take shorter or longer depending on your schedule or the MRI scanner schedule.

Before you begin the main part of the study...
You will need to have the following screening exams/ tests/ procedures to find out if you can be in the main part of the study.

STUDY VISIT #1:
SCREENING PROCEDURES:

- Medical and Mental Health History: A study investigator will ask you questions in order to complete a health screening questionnaire. This questionnaire screens for psychiatric or neurological illness; major health problems, including liver disease; and medications that can affect the mind or mental processes.
- MRI safety: We are also screening for conditions that are incompatible with MRI scanning, including claustrophobia or the presence of certain metals inside your body.
- Current medicine use: Researchers will also ask you about any medicines you take. The researcher will review drugs that would prevent you from being in this study.
- Questionnaires: Researchers will ask you to complete computerized questionnaires and behavioral tests that evaluate different factors that could affect your behavior, your thinking, and your movements.

POST-SCREENING REFERRAL:

- Blood drawing (venipuncture) at Quest Diagnostics: You will be asked to give a blood sample for lab tests that check your blood counts and liver function. You can be provided with a blood draw form by US mail or secure email, whichever you prefer, that you may take to a blood draw location run by Quest Diagnostics. Approximately 2 teaspoons of blood will be drawn by inserting a needle into a vein in your arm for these tests.

During the main part of the study...
If the screening exams and tests show that you can continue to be in the study and you choose to continue, the following describes what will happen at the next two visits.

STUDY VISIT #2:
-10 minutes: Researchers will ask you to provide a urine sample in order to perform a urine test for drugs of abuse, such as cocaine, amphetamine, methamphetamine, tetrahydrocannabinol (THC), and opiates **. Researchers will also ask you to blow into a tube attached to a small device that will test for alcohol (the Breathalyzer test) **. If you are a woman who is able to become pregnant (i.e. you have had your first menstrual period and have not yet reached menopause), your urine will be tested to make sure you are not pregnant **. Because the medication in this study can potentially affect a fetus, pregnant women may not participate in this study. If you test positive for drugs of abuse or for alcohol, or if you are pregnant, you cannot continue to participate in this study.

** Information from the urine test, breathalyzer test, and pregnancy test will be used only for screening purposes and the samples will not be stored for future analyses. The results will not be recorded or communicated to anyone other than you or the study team.

-5 minutes: Researchers will measure your blood pressure and pulse. Researchers will ask you to provide a saliva sample so that we can get information about specific genes that are related to dopamine metabolism. You will also complete brief baseline tests that assess your memory, mood, and movements (a "mini-battery").

0 minutes: We will give you one capsule of tolcapone (200mg) or placebo (a pill that has an inactive substance in it), according to random assignments. The pill you will get will be chosen by a coin flip. The capsule will also include a B vitamin called riboflavin to make sure no one can tell who gets the study drug by the color of your urine. The riboflavin will cause a mild fluorescent change in urine color that is temporary and harmless.

+60 minutes: Researchers will repeat the mini-battery.

+90 minutes: You will have a Magnetic Resonance Imaging (MRI) exam done. The MRI scanner measures small changes in magnetic fields produced in your brain and generates images of the human brain. For the MRI exam, you will be asked to lie down on a platform that can be slid into the center of a large magnet. A plastic coil will be placed around your head and foam pads will be placed to limit head movement during the study. You will then be slid into the magnet and asked to lie still for approximately 90 minutes while the MRI images are acquired. The machine makes loud noises while it takes the images, and some people may find it claustrophobic. When you are inside the MRI scanner, behavioral testing will evaluate your memory, decision making, and other brain functions. During the memory task, digital audio recordings will be made of your verbal responses.

+210 minutes: You will repeat the mini-battery and an additional blood pressure reading will be taken. You will then be asked to do pencil-and-paper and computer-based tests that present words and pictures and ask you to make responses. For example, you will be asked to remember lists of words, to sort letters and numbers into different categories, and to choose how to divide money between yourself and another person.

+300 minutes: You will complete the final mini-battery, ending your testing day.

STUDY VISIT #3:
Within approximately 3 weeks of the study visit #2, you will be asked to return for the third study session. Procedures during this visit will be identical to the procedures during study visit #2, except that you will receive the study capsule (either tolcapone or placebo) that you did not receive at study visit #2, and you will not need to provide a saliva sample again at this visit.

GENERAL INFORMATION ABOUT STUDY PROCEDURES:

Procedures related to behavioral testing outside the MRI scanner:

- You will be seated at a computer in a well-lit room. Extraneous sound will be minimized.
- You will receive instructions prior to beginning each task. You will be told that the cognitive task will involve presentation of images and/or words on a screen. You will be asked to respond to certain visual stimuli by pressing a button on a keypad. Visual or auditory feedback may be presented, especially during task training.

- To ensure that you are able to participate effectively, you will be familiarized with performance of the task via practice trials. All stimuli will be shown at comfortable lighting and sound levels.
- You will be given frequent breaks during testing. Testing will last approximately 45 minutes, depending on the number of breaks and your pace during testing.

Procedures related to behavioral testing inside the MRI scanner:

- A metal scanner will be used to ensure that you have removed all metal containing items.
- Due to the noise in the scanner, you will be provided with earplugs. Additionally, a vitamin E capsule will be taped to the right side of your forehead to permit researchers to easily distinguish left from right sides on the obtained MRI images.
- You will be walked into the scanner room itself, where you will be provided with headphones that will allow us to communicate verbally during breaks in scanning. You will then lie on the scanner bed, facing upward. A foam pillow will be placed under your head, and a foam block will be placed under your knees to reduce strain on the low back, unless you prefer lying down without it. Once you are comfortable, we will apply additional padding around the head to ensure comfort and to provide a reminder that you should minimize head motion.
- The MRI imaging coil will then be placed around your head. This coil will not contact you. A mirror will be attached to the top of the coil, to allow you to visualize a screen placed behind you in the rear of the scanner.
- You will be given one item for each hand: a squeeze ball for the left hand, and a button box for the right hand. The squeeze ball, if pressed, will cause a loud alarm to sound in the MRI control room, alerting us to stop MRI scanning. You will use the button box to provide responses during tasks. In addition, if you are comfortable with the fit, we will apply a pulse oximeter to a finger on your left hand, as well as a respiratory measurement band around your chest, to monitor heart and respiratory rates during scanning.
- You will be moved into the center of the MRI scanner. The lights in the scanner room will be dimmed, and subsequent communication will take place through your headphones and a microphone positioned above you in the MRI scanner.
- A sequence of MRI images, each requiring approximately 5-10 minutes, will then be obtained. The total duration of the scan session will be approximately 90 minutes, depending on factors including the length of your breaks between scans, how still you are able to remain, and the total duration of the MRI scans themselves.
- After completion of the scanning session, you will be removed from the magnet bore and return to the scanner control room.

Study time: Your study participation will take a total of approximately 13 hours spread across the screening visit and the 2 testing visits. An initial screening visit including behavioral questionnaires and preliminary behavioral testing, and accounting for time related to the blood draw, will last approximately 3 hours. Each testing visit will include approximately 2 hours of behavioral testing, 1.5 hours of MRI scanning, and 1.5 hours for breaks and the other study procedures just described, such as the urine and Breathalyzer testing. Each testing visit will last approximately 5 hours.

Study location: These study procedures will take place remotely via phone or videoconferencing platform Zoom, and on the UC Berkeley campus or the UCSF Research Clinic.

Benefits

There will be no direct benefit to you from participating in the study. However, this study will potentially allow us to learn more about how dopamine affects decision making, and we hope that this information will help in the future treatment of individuals with decision making disorders. You may also gain some

insight into the scientific process of learning about brain function, and you may note changes in your performance on the behavioral tasks. In addition, you may benefit psychologically from knowing that you are participating in research designed to benefit other people.

Risks/Discomforts
Possible risks, discomforts, and/or side effects related to the study procedures include:

- **Study drug risks:** Tolcapone may have side effects. You may have nausea, headache, anxiety, dizziness, a slight drop in blood pressure or other side effects after taking this drug. These effects are generally rare and mild when they do occur. If you have any of these side effects, they should pass fairly quickly (within 24 hours) and will not cause any permanent problems. If you feel sick, a physician who will be closely supervising this study will examine you. The physician may ask you to lie down, drink liquids, or stop the study. If you are experiencing side effects that make it difficult for you to drive when the session is over and you are unable to arrange your own escort home, we will provide one to accompany you home, a taxi, or BART fare. To minimize the possibility of potential nausea from the drug, we will ask you to have a light meal about one hour before you come in for the study. Additionally, blood pressure will be monitored throughout the study.

  In the greater than 40,000 patient years of tolcapone use, 3 patients with Parkinson's disease who were using tolcapone daily died because of liver failure associated with tolcapone. There have been no cases of liver injury reported in a healthy person after only a single dose of this medication. However, if you have a history of liver problems, you cannot be in this study.

  We will also ask you not to participate in this study if you have recently used medications that affect dopamine levels (such as tolcapone itself or any of the following: levodopa/carbidopa, entacapone, amantadine, pergolide, pramipexole, ropinirole, selegeline, isocarboxazid, phenelzine, tranylcypromine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, dextroamphetamine, dexmethylphenidate, methylphenidate, cocaine, or methamphetamine).

  There are no known risks of placebo, and there are no known risks of riboflavin at the current dose other than mild and temporary discoloration of the urine.

- **MRI scan risks:** The magnets in the MRI scanner are extremely powerful and will attract any metallic objects brought into the MRI room, so you must be careful to leave anything made of metal outside the room. People with pacemakers or certain metallic implants in their body cannot participate in this study. You will be screened for these conditions.

  While there are minimal risks from MRI as it is to be performed and MRI scanning itself is painless, participation may involve some discomfort. In particular, you may be bothered by the loud noise during the study that is due to beeping and hammering sounds made when the scanner is collecting measurements. Disposable earplugs will be provided to diminish the noise. Also, some people become claustrophobic while inside the scanner. (Individuals with a history of claustrophobia will be excluded from the study.) You may also experience stimulation of the nerves in your body, which feels like a gentle tap or sensation of mild electric shock.

  We will be able to communicate with you during the session via an intercom system. If you feel uncomfortable in the scanner for any reason, please let us know and we will stop the experiment.

- **Physical risks:** There are no risks associated with measurement of your blood pressure and pulse except the possibility of brief unanticipated physical or emotional discomfort.

- **Psychological risks:** The behavioral procedures have been used extensively in previous research. The pictures and words are presented at a comfortable lighting level; the sounds are transmitted at a pleasant volume; and the written and/or button press responses are designed to minimize physical effort. It is possible that you may become bored, anxious, or frustrated when completing these tasks. It is also possible that when you are answering questions about emotions, you may feel as though you would like to discuss these emotions further with a counselor. If you would like to speak with a counselor and you do not already have a private provider, resources are available. UC Berkeley faculty and staff may contact the Employee Assistance Program at 510-643-7754. UC Berkeley students may contact Counseling and Psychological Services at 510-642-9494. Anyone may contact the National Suicide Prevention Hotline at 800-273-8255. We regret that this research study is not able to provide individual feedback about these issues.

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, or very rarely, infection.

- **Urine testing risks:** False positives in urine toxicology drug or pregnancy testing might occur, which may make you ineligible to participate in the study and may lead to anxiety or discomfort.

- **Saliva sample risks:** It may be uncomfortable to generate enough saliva to fill a sample tube. You will be provided with privacy and as much time as you need while providing this sample.

- **Genetic risks:** The genetic tests included in this study do not currently have any known clinical applications and they are not obtained with any clinical purpose. However, in the future it is theoretically possible that these genes could be linked to a clinical condition. If so, this link might cause psychological or social risks if the information is unexpected or unwanted, or the knowledge might alter reproductive decisions, employability, or insurability.

- **Social risks:** There are no known social risks of these studies.

- **Economic risks:** There are no known economic risks of these studies. You will be reimbursed for your participation, as noted below.

- **Unknown Risks:** The experimental procedures may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- **Breach of confidentiality:** As with all research, there is a chance that confidentiality could be compromised; however, we are taking precautions to minimize this risk.

Confidentiality

Your study data will be handled as confidentially as possible. If results of this study are published or presented, individual names and other personally identifiable information will not be used.

To minimize the risks to confidentiality, we will code your research data without using your name. Dr. Hsu and Dr. Kayser will hold the key to the code. The hard-copy key to the coded information is kept in a separate location under lock and will not be placed on a removable medium. Dr. Hsu Dr. Kayser, N.P.

Weinstein, and their research assistants will have access to the hard-copy key. The key will be destroyed after 5 years after the close of the study. We will add your information to a database. We protect these data on the computer with passwords. We will store your information, research data, and related records in locked offices. Digital audio recordings will be retained on a password-protected device, be transcribed within 1 week after they're obtained, and will be erased/destroyed after transcription is complete.

Your personal information may be given out if required by law. Authorized representatives from the following organizations may review your research data for purposes such as monitoring or managing the conduct of this study:

· Sponsor: National Institute of Mental Health (NIMH)
· University of California
· Food and Drug Administration (FDA) and other government agencies involved in keeping research safe for people.

We will keep your study data as confidential as possible, unless it is certain information that we must report for legal or ethical reasons, such as child abuse, elder abuse, or intent to hurt yourself or others.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health (NIH). With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

Exceptions: A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing certain information about you for legal or ethical reasons. For example, we will report information about child abuse, elder abuse, or intent to hurt yourself or others. If an insurer, employer, or other person obtains your written consent to receive research information, we cannot use the Certificate to withhold that information. In addition, the Certificate may not be used to withhold information from the federal government needed for auditing or evaluating federally funded projects or information needed by the FDA, e.g., for quality assurance or data analysis.

Retaining research records: When the research is completed, we will save the study records and MRI images for possible use in future research done by ourselves or others. We will retain study information that includes personal identifiers for up to 5 years after the study is over. Signed consent forms will be retained for 10 years after the end of the calendar year in which the research is completed. All DNA extraction will be limited to the duration of the current study. Samples will be discarded after the DNA has been measured or extracted. De-identified study data, such as the results of behavioral tests and MRI exams, will be retained indefinitely. This de-identified information could be used for future research studies or distributed to other investigators for future research studies without additional informed consent from the subject or the legally authorized representative. The same measures described above will be taken to protect confidentiality of this data.

Clinically relevant research results, including individual research results, will be disclosed to subjects. In particular, the MRI scan of your brain is for research. The MRI pictures for this study are not meant to evaluate your health. Your MRI pictures will not receive any routine clinical review. As a result, researchers may not notice all abnormal findings. However, researchers may find an unexpected abnormality when they review your MRI pictures. If so, they will notify the researchers in charge of this study, Ming Hsu, Ph.D. and Andrew Kayser, M.D. Ph.D. Dr. Kayser is a physician who specializes in

neurology. He routinely looks at MRI pictures. If necessary, he may ask another specially trained physician (a radiologist) to help you obtain a more complete review of your MRI scan. The researcher in charge of this study will discuss these possible problems with you. Researchers will cover your name when the radiologist checks your MRI pictures to find out if any clinical health condition is present. If the radiologist thinks a health problem is present, we will give you a copy of the MRI picture. You can take the MRI picture to the physician of your choosing, at your expense. If you prefer, we can send the pictures electronically; there is a small risk that someone else could view electronically sent files. Research results, including individual research results, will otherwise not be disclosed to subjects.

Information obtained from your biospecimens, such as blood or saliva, may be used in this research or other research, and shared with other organizations. However, the biospecimens themselves will be discarded once the information is obtained. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

If you withdraw from the research, the data collected about you up to the point of withdrawal will remain part of the study and may not be removed from the study database per FDA regulations.

The research will not include whole genome DNA or RNA sequencing.

Alternatives
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. Your alternative is not to take part.

Compensation/Payment
In return for your time and effort, you will be paid for taking part in this study. You will receive $12 per hour for your time outside the MRI scanner, and $20 per hour for your time inside the MRI scanner. You will get an additional payment of $40 for the blood draw. You may complete tasks that include monetary bonuses up to a total of $40. You will not be reimbursed for travel expenses. Subjects who complete all 3 sessions can expect to earn approximately $250-300. A check will be mailed to you about 6 weeks after you have finished the study. If you do not complete the study, you will receive payment only for those parts of the study that you have finished.

Costs of Study Participation
You will not be charged for any of the study activities. If you elect to receive text messages from research study personnel, you may incur standard text message charges, depending on your cellular plan.

Treatment and compensation for injury
It is important that you promptly tell the researcher, Ming Hsu, Ph.D., if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him at 510-642-6000.

If you are injured as a result of taking part in this study, University of California will provide necessary medical treatment. The costs of the treatment may be billed to your insurer just like other medical costs, or covered by the University of California or the study sponsor, the National Institutes of Health, depending upon a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information, call OPHS at (510) 642-7461.

Rights
Participation in research is completely voluntary. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

Re-Contact
You may be re-contacted to see if you are interested in participating in other research studies. You are under no obligation to take part in other research studies if you do not want to do so. Do you give your permission for us to re-contact you in the future about participating in other studies?

☐ Yes ☐ No

Questions
If you have any questions or concerns about this study, you may contact Dr. Ming Hsu at 510-642-6000. You may also contact him as follows: Dr. Ming Hsu, Helen Wills Neuroscience Institute, 132 Barker Hall, Berkeley, CA 94720-1650. Email: mhsu@haas.berkeley.edu.

If you have any questions or concerns about your rights and treatment as a research subject, you may contact the office of UC Berkeley's Committee for the Protection of Human Subjects, at 510-642-7461 or subjects@berkeley.edu.

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CONSENT

You will be given a copy of this consent form and of the Medical Research Subject's Bill of Rights to keep.

If you wish to participate in this study, please sign your name below.

_____	_____	_____
Participant's Name *(please print)*	Participant's Signature	Date