University of California, San Diego
Consent to Act as a Research Subject

Toward understanding dopamine receptor contributions to prediction error and reversal learning in anorexia nervosa

Introduction

Dr. Guido K.W. Frank is conducting this research and asking for your consent to participate. This section provides a summary of important information. The rest of the form provides additional details.

- Research is voluntary- whether or not you join is your decision. You can discuss your decision with others (such as family, friends or another physician).
- You can say yes but change your mind later.
- If you say no, we will not hold your decision against you.
- Your decision will not affect your health care or any other benefits you may be entitled to.
- You can say no even if the person inviting you is part of your healthcare team.
- Please ask questions or mention concerns before, during or after the research.

We are trying to learn more about the impact of medication on the brain reward systems. We are trying to gain more information about what happens in the brain when we receive so called rewards, that is things people usually like and look forward to, and how medication may enhance or diminish the brain's response to these rewards. This study may better help us understand treatments for anorexia nervosa.

You will first undergo several procedures to determine if you are eligible for the study including questionnaires, interviews, and blood tests. If you are eligible, you will be scheduled for 3 MRI brain scans spaced about 3 days apart. Before each scan, you will take a study medication, eat a standardized breakfast, complete questionnaires and then complete a brain scan that lasts about one hour where you will receive sweet and neutral taste solutions and play a learning game. Each study visit day will last up to 4 hours.
The most commonly expected risks of the study are discomfort from filling out the questionnaires and being in the MRI scanner for about an hour. The most commonly expected medication risks of the study are feeling tired or dizzy.

The most serious risks of the study may include allergic reaction to the study medications or a low heartbeat. The likelihood of this occurring after one single administration of the drug is very low and we will exclude individuals with risk factors for those conditions .

This is not a treatment study. The only alternative is not to participate in the study.

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Please take your time to make your decision. Discuss it with your family. Additional, detailed information about this research is provided below. Please feel free to ask questions before signing this consent.

Why have you been asked to participate, how you were selected, and what is the approximate number of participants in the study?
You have been asked to participate in this study because you are a healthy control and at normal weight or you are underweight and struggle with anorexia nervosa. There will be approximately 104 participants in this study.

How much time will each study procedure take and how long will the study last?
You will be in the study for up to 3 months (depending on scheduling). This will include the initial phone screening, questionnaire packet, psychiatric assessment, blood draw, electrocardiogram (EKG) and 3 MRI scans spaced about 3 days apart.

You can stop participating at any time. However, if you decide to stop from participating in the study, we encourage you to talk to the research doctor.

What will happen to you in this study and which procedures are standard of care and which are experimental?
In addition to the information at the beginning of this form, here are some additional details about will happen to you if you agree to be in this study.

If after initial screening, you are invited to join the study, and if you provide your Informed Consent on this Form, then you will be assigned to one of two groups.

- The first group will consist of persons with anorexia nervosa. Anorexia nervosa is an eating disorder associated with intense fear of weight gain, food refusal, and severe weight loss.
- The second group, which we call a control group, will consist of persons who are within average weight range and appear to be in generally good health.

If you are recruited from the community, you will participate in 2 phone calls at the beginning of the study.

- At the first phone call, we will ask you some basic questions about your physical condition and general health as well as review the consent form with you (10 minutes).
- If you qualify and agree to participate further in the research, we will mail you a paper copy of the consent and several questionnaires to complete (it will take about an hour to complete the questionnaire packet).
- When we receive the questionnaires back, you will get a second phone call from us where we will let you know if you qualify and can continue in the study. If you don't or if we don't hear back from you in 3 months, any information we collected about you will be destroyed.
- If you qualify and agree to go on with the study, we may do one more screening questionnaire with you at the second phone call (about 30 minutes). If you qualify and agree to continue in the research, we will schedule an in person visit.

If you are recruited from UC San Diego Health Eating Disorders Center for Treatment and Research, we will ask you screening questions in person when we meet with you.

- If you qualify and agree to participate further in the research, we will provide you with a paper copy of the consent and several questionnaires to complete (it will take about an hour to complete the questionnaire packet).
- When we receive the questionnaires back, we will meet you in your treatment program or call you to let you know if you qualify and can continue in the study.
- If you qualify and agree to go on with the study, we may do one more screening questionnaire.

If you join the study, you will complete the following:

1. Screening and Assessment (Screening Visit, 60 to 90 minutes, in-person)

- We will ask you about your psychiatric and medical history before entering the study. Here we will ask you questions about what illness you may have had. We will also ask you personal questions about how you have been feeling including questions about any times when you may have been depressed or gotten very anxious or afraid of certain situations. You will be asked questions about trauma that may have occurred to you. You may decline to answer any questions.
- In addition, we will ask you about your drug and medication history. If you are taking certain medications, you may not be able to participate in this study. Throughout your participation in this study, it is important that you do not drink any alcoholic beverages or take any drugs or medications unless you notify the research investigators.
- We will have you complete a swallow test to make sure that you will not have difficulty swallowing the study medication. For this, you will be given an empty medication capsule that will be the same size as the one you will take the morning of each Study Visit.
- If you qualify for the study, you will be scheduled for the brain imaging study.

2. Pre-Scan Blood Draw and Electrocardiogram(EKG) (Pre-Scan Visit, 60 minutes, in-person)

In order to make sure it is safe for you to have the study medication and complete the MRI scans, you will be asked to complete a Pre-Scan Visit no more than one week before your scheduled Study Visit 1. At this visit you will be asked to complete the following:

- A blood draw that will measure your electrolyte and kidney function. It will also tell us if you are pregnant (about 2 tablespoons of blood will be taken).
- An electrocardiogram (EKG) that will measure the electrical activity in your heart. For this procedure sensors (electrodes) will be placed on your chest and limbs and the machine will measure the electrical activity of your heart.

If you have abnormal test results you may be withdrawn from the study.

3. Brain Imaging Study (Study Visit 1, Study Visit 2, Study Visit 3; 4 hours each study visit, in-person)

You will complete 3 brain scans that are spaced about 2 – 4 days apart.
The brain scans are done using a machine called magnetic resonance imaging (MRI) scanner. This is a large magnet that can be used to study the brain. This type of machine is very commonly used in hospitals to detect whether someone has an injury for instance in the brain or other body parts. This procedure does not involve any radiation and is seen as very safe.

- On the morning of each of the brain imaging studies, we ask you to be at the Sharp and Children's MRI Center, 7910 Frost St Suite 110, San Diego, CA 92123, between 6 to 7 am.
- A urine pregnancy test will be conducted on Study Visit 1 regardless if you believe there is any possibility of you being pregnant. If you are pregnant or nursing, you will not be able to participate in this study.
- After you complete the pregnancy test and if the test is negative, you will be asked to take one of the study medications (placebo, amisulpride, or bromocriptine; order is randomized). The Principal Investigator and research staff are blinded to which medication you will be given on each Study Visit. The order in which you will receive the study medication the morning of the scan will be assigned by chance. Neither you nor the researcher can choose the order to which you will receive the medications. The research staff will administer the oral medication at the start of your breakfast and the fMRI scan will begin three hours later.
- We will provide you with a standard breakfast or you will eat according to your meal plan if you are in an eating disorder treatment program.
- You will be asked to complete several questionnaires that ask about your mood, food cravings, and eating behaviors.
- You will be asked to test sugar solutions rate those for your personal sweetness and pleasantness experience. You will be testing various sugar solution strengths. In order to test that, you will be presented with 9 small samples of the solutions with about ½ teaspoon (2 ml) that you will swallow. The test for solutions will take about 10 minutes.
- Prior to each MRI scan you will be familiarized with tubes that deliver taste stimuli to your mouth. You will be shown how to position the tubes in your mouth and to wipe your tongue once around in your mouth after each taste application. You cannot participate in the MRI part of the study if you have difficulty with this procedure.
- A picture of your brain will be obtained using a Magnetic Resonance Imaging Scanner. One type of picture called MR scan will show us the anatomy of your brain. The other pictures show us how much blood is flowing through your brain during the time in the brain scanning machine.
    - For this, you will be placed in a large donut-like machine (MR scanner).
    - The scanning will take about 60 minutes.
    - Your head will be placed in a special helmet-like "head-holder" to keep your head still.

  During each MRI scan, you will be asked to complete several computerized tasks:
    - You will be asked to hold the taste tubes in your mouth. At various intervals, small amounts (1 ml, which is about 1/5 of a teaspoon) of liquids of either sugar water or a tasteless solution will be delivered into your mouth. Before each taste solution you will see an abstract colorful picture on goggles that you are wearing in the scanner and you will be asked to predict what solution will follow each abstract picture by pressing a button on a button box. This task will take 28 minutes.

- You will be asked to play a game where you will learn rules what buttons to push in response to visual cues. These rules will change throughout the task. This task will take about 20 minutes.

Altogether, assessments will take about 3 hours, the blood draw and EKG will take about an hour and each brain imaging session including breakfast and questionnaires will take about 4 hours. Total study duration therefore is about 16 hours on 5 different study days over about 2 weeks.

Study Procedures Chart (Subjects from Community)

	Initial Screening (Phone)	Detailed Eligibility Screen (Phone)	Screening Visit (In-Person)	Pre-Scan Visit (In-Person	Study Visit 1 (In-Person)	Study Visit 2 (In-Person)	Study Visit 3 (In-Person
Initial Screening	**X**						
Informed Consent (through mail)		**X**					
Questionnaire Packet (through mail)		**X**					
Biological Screening Form		**X**					
In-Person Consent and Meeting with PI			**X**				
Mental Health Interview			**X**				
Medication Swallow Test			**X**				
Blood Tests & EKG				**X**			
Pregnancy Test					**X**		
Taste Test					**X**	**X**	**X**
MRI Scan					**X**	**X**	**X**
Scan Questionnaires					**X**	**X**	**X**

Study Procedures Chart (Subjects from UC San Diego Health Eating Disorders Center for Treatment and Research

	Consent Visit	Screening Visit	Pre-Scan Visit	Study Visit 1	Study Visit 2	Study Visit 3
Initial Screening	**X**					
Informed Consent	**X**					
Questionnaire Packet		**X**				
Consent and Meeting with PI		**X**				
Mental Health Interview		**X**				
Medication Swallow Test		**X**				
Blood Tests & EKG			**X**			
Pregnancy Test				**X**		
Taste Test				**X**	**X**	**X**
MRI Scan				**X**	**X**	**X**
Scan Questionnaires				**X**	**X**	**X**

Additional Optional Procedures

The following are additional optional study procedures that you are being asked to consider. You may choose to participate in any, or none, of the following procedures. Your decision to participate, or to not participate, in these additional procedures will not affect your ability to participate in the main study you agreed to above.

Consent to be Contacted for Future Research Studies (Optional)

There may be future studies that you are eligible to participate in. Please initial below whether you agree or do not agree for us to contact you about participating in future studies.

Initial next to your choice:

_____ I agree to be contacted for future research

_____ I **do not** agree to be contacted for future research

Consent to Allow the Research Team to Share your Information with UC San Diego Health Eating Disorders Center for Treatment and Research (Optional)

You may also opt-in to allowing the research team to share your information in the following manner below.

Initial next to your choice:

_____ I agree to allow the data collected to be shared with my health provider at UC San Diego Health Eating Disorders Center for Treatment and Research (e.g. to assist clinicians and treatment teams in assessing which strategies might be most effective based on your current measures).

_____ I **do not** agree to allow the data collected to be shared with my health provider at UC San Diego Health Eating Disorders Center for Treatment and Research (e.g. to assist clinicians and treatment teams in assessing which strategies might be most effective based on your current measures).

Initial next to your choice:

_____ I agree to allow the data collected to be shared with researchers/research teams at UC San Diego Health Eating Disorders Center for Treatment and Research for use in other eating disorder research studies.

_____ I **do not** agree to allow the data collected to be shared with researchers/research teams at UC San Diego Health Eating Disorders Center for Treatment and Research for use in other eating disorder research studies.

What risks are associated with this study?
Participation in this study may involve some added risks or discomforts. In addition to the risks described at the beginning of this form.

1. Risk of filling out the questionnaires

You may experience some psychological discomfort or fatigue when filling out questionnaires. You do not have to complete the questionnaires in one sitting. You can choose not to answer any question that makes you uncomfortable.

2. Risks of the scanner

While in the scanner, you may experience a gagging response or nausea/gastrointestinal discomfort to certain tastes.

If you are uncomfortable with the testing procedure, the study can be stopped at any time. If we discover that you describe emotional distress, then we will evaluate if you are in need for a referral for professional help. Such a referral may range from counseling to referral to the authorities for emergency treatment.

3. Risk of loss of confidentiality

Some of the information collected, e.g. whether you have used illegal substances, were to become public, it may place you at risk for criminal or civil liability or may be damaging to your ability to get a job, affect your personal reputation, or have otherwise unforeseen consequences.
In order to minimize this risk, all of your data will be kept in locked cabinets or in databases with secured passwords with access restricted to the PI and his research staff.

4. Risk of an MRI

You should NOT have an MRI if you have <u>metal</u> or <u>electronic devices</u> inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.
The most common side effects of having an MRI are the following

- You may experience flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. This usually goes away after a few minutes.
- There is a risk of muscular aches from lying on your back for a total amount of about 60 minutes in the scanner.
- Banging noises that the MRI machine makes while taking pictures of your brain are loud. You will be wearing headphones and ear plugs to minimize this noise.
- Muscle twitches during the magnetic resonance imaging procedure may occur.
- There are no known harmful effects from the magnetic resonance imaging, but some people undergoing this procedure may become anxious and afraid of closed spaces. If this happens to you, you can stop this procedure at any time.
- If you are pregnant or think you may be pregnant, you should not take part in this research. If you have any metal clips or plates in your body or a pacemaker, you should tell the investigator about it. We will carefully screen you for any metal in your body.

Before going into the scanner we will carefully screen you to make sure you are safe to have an MRI scan. Before the scan starts we will give you pillows and a blanket to make you more comfortable. The ear plugs and headphones will muffle the noise and protect your ears. We will check on you throughout the scan to make sure that you are comfortable and will give you a buzzer that alerts us of an issue. You can stop the scanning procedures at any time.

5. Risk of Medication

Bromocriptine. This medication is used to treat Parkinson's Disease and Type 2 diabetes. It has previously been used in brain imaging studies like this.

The most common risks from using this medication for prolonged use include: nausea, headache, stomach upset, dizziness, drowsiness, feeling faint or fainting, and suddenly falling asleep.

Serious side effects from using this medication for prolonged use can include: heart attack, stroke, and pulmonary fibrosis (lung disease).

After the one-time application you might feel at most some nausea, headache or dizziness. The other side effects are in the context of prolonged prescription and not after single dose which the study will use.

Certain conditions may interact with this medication. You should let your study doctor know if you have syncopal migraines (experience fainting with migraines), uncontrolled hypertension (high blood pressure), pheochromocytoma (adrenal gland tumor), prolactinoma (overproduction of the hormone prolactin from a noncancerous pituitary tumor), breast cancer or a hypersensitivity or allergy to bromocriptine. You should let your study doctor know if you have a history of long QT syndrome (heart rhythm condition that can potentially cause fast, chaotic heartbeats) or family history of sudden death or long QT syndrome. If you have a history of seizures or seizure disorder you will not be included in the study.

Amisulpride. This medication has been used in Europe as an antipsychotic medication. It has previously been used in brain imaging like this in the US.

The most common risks from using this medication for prolonged use include: fever, excessive sweating, change in heart rate, chest pain, swelling, pain, and redness in the legs, increased frequency of infections, skin allergy, seizures, restless legs, twitches in the tongue and face, trembling, excessive salivation, constipation, decreased libido (sex drive), weight gain, amenorrhea (absence of menstruation), agitation or anxiety, tardive dyskinesia (a condition that causes involuntary repetitive movements) and neuroleptic malignant syndrome (disease that affects the nervous system and causes symptoms like a high fever and muscle stiffness).

After the one-time application you might feel at most some nausea.

Certain conditions may interact with this medication. You should let your study doctor know if you have pheochromocytoma, prolactinoma, Parkinson's Disease, breast cancer or a hypersensitivity or allergy to amisulpride.

We will carefully monitor you throughout the Study Visit. We will measure your blood pressure and heart rate and will check for any symptoms of an adverse reaction to the medication. If these symptoms do not go away, we will get you emergency care as needed.

6. Risk of blood draw

In this study we will need to get about 2 tablespoons of blood from you. A certified phlebotomist will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin. There is also a slight possibility of infection. The phlebotomist will apply pressure to the needle site in order to reduce the possibility of bruising.

7. Risk of Electrocardiogram (EKG)

There is a small risk that you will get a skin rash where electrodes are placed.

There may be risks associated with this study, which are currently unforeseeable.

For more information about these risks and side effects, ask your study doctor.

Should we identify during the screening process or interviews an acute danger to others or yourself we will be obligated to contact emergency services or the police department to ensure that you are safe.

Are there risks to the reproductive system or a developing fetus?
The effects of the MRI procedures and medications may pose some unforeseeable risks to a developing fetus. For this reason, participants in this investigational study should not become pregnant and we require that all participants take a serum pregnancy test the week before the first MRI and a urine pregnancy test the morning of Study Visit 1 before the MRI scan. If you have a positive pregnancy test, we will withdraw you from the study. If you become pregnant or if there is any chance of pregnancy (e.g., late menstrual period), please contact the study personnel immediately so that we may provide medical assistance and counseling.

What benefits can be reasonably expected?
There are no known benefits to taking part in the study. This study is designed for the researcher to learn more about how the brain responds in individuals with anorexia nervosa compared to normal weight individuals when getting rewards that are usually considered pleasant and the effect of medication on this brain response. This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

What happens if you change your mind about participating?
If you decide that you no longer wish to continue in this study, you may contact Dr. Frank or his research staff.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

Can you be withdrawn from the study without your consent?
The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

Will you be compensated for participating in this study?
In compensation for your time and travel:

- You will be paid $25 for the Questionnaire Packet and Initial Screenings.
- You will be paid $25 for the Psychiatric Interview.
- You will be paid $25 for the Blood Draw & EKG.
- You will be paid $150 for each MRI Scan/Study Visit.
- You will be reimbursed up to $5 for parking for the Pre-Scan Visit.

This will add up to a total of $530 if you complete all the visits. If you leave the study early, or if we have to take you out of the study, you will be paid only for the visits you have completed.

If there are any issues that arise after you have arrived at the MRI Center on the day of your Study Visit (such as a problem with the MRI machine) that require rescheduling the Study Visit, we will compensate you an additional $100 for your time.

If you are excluded prior to Study Visit 1, your compensation will be in the form of an electronic gift card to Amazon or Target.

It is important to know that payments for participation in a study is taxable income and we will report your compensation to the IRS. If you are excluded or stop your participation in the study prior to completing the first MRI Scan/Study Visit, it will not be necessary for us to report your electronic gift card amount to the IRS.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care needed to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?

Research records will be kept confidential to the extent allowed by law. Every reasonable effort will be made to keep your records confidential. All data will be kept in a locked file cabinet only accessible to the study team, and on a password protected computer. All direct identifying information such as name and medical record number will be destroyed at the end of the study.

While you are in this study all related records may be made available to:

- The funding sponsor (National Institute of Mental Health)
- The UCSD Institutional Review Board (for the protection of human subjects in research)
- Other regulatory agencies responsible for overseeing research, such as the federal Office for Human Research Protections
- The Food and Drug Administration (FDA)
- The study doctor and his research team

This research is covered by a Certificate of Confidentiality from the National Institute of Mental Health (NIMH). Researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research *unless* there is a federal, state, or local law that requires disclosure (such as to report child abuse, elder abuse, intent to hurt self or others, or communicable diseases), you have consented to the disclosure, including for your medical treatment; or it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institute of Mental Health, which is funding the project or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA). You should also understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the research to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document including research data in the medical record.

Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

Personal identifiers will be removed from the information or biospecimens collected as part of the research. After such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

If the study results are published or presented, you will not be identified.

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

Will you receive any results from participating in this study?
You may request a copy of the in-depth psychiatric interview from the investigator, which may be helpful to your treatment provider. You may also request to review this interview with the PI. You will not receive any other results from participating in this study.

Who can you call if you have questions?
This study has been explained to you and your questions have been answered. If you have other questions or research-related problems, you may reach Dr. Guido Frank at 858-246-2053.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent
You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____ _____
Subject's signature Date

_____ _____
Signature of the person conducting the informed consent discussion Date

SUBJECT'S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. A subject in a research study or someone, who is asked to give consent on behalf of another person for such participation, has the right to the following:

1. Be informed of the nature and purpose of the research.

2. Be given an explanation of all procedures to be followed and of any drug or device to be used.

3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.

4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.

5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.

6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.

7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.

8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.

9. Be given a copy of the signed and dated written consent form.

10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your rights as a research subject, please contact your research doctor or the UCSD Human Research Protections Program at 858-246-HRPP (858-246-4777).