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Identifying neurophysiological mechanisms of susceptibility to estradiol fluctuation and irritability symptoms in the menopause transition: An experimental approach

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University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants
Consent Form Version Date: 04/09/2024
IRB Study # 21-3395
Title of Study: Identifying neurophysiological mechanisms of susceptibility to estradiol fluctuation and irritability symptoms in the menopause transition: An experimental approach
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Concise Summary

Women in the menopause transition (perimenopause) have a significantly greater risk of developing depression. For most women with depressive symptoms during the menopause transition, irritability not "depression" is their primary source of impairment and distress. While most women are exposed to erratic hormone changes in the menopause transition, about 40% are susceptible to the emergence of mood symptoms tied to changes in estrogen. Estrogen modulates brain systems associated with depression; has anti-depressant/anti-anxiety effects; and regulates brain networks involved in depression. Thus, the purpose of this study is to understand the biological mechanisms underlying the relationship between estrogen and the emergence of irritability symptoms during the menopause transition. Study duration will last 16 weeks. Participation will include an enrollment session with questionnaires on your current mood and stress, frequent hormone measurements (urine) and mood assessments at your home, and three weeks of wearing both an estrogen patch (active) and placebo (no active drug) patch in a randomized order. You will also complete 3 laboratory sessions that involve recording your brain activity while you perform several computer tasks. There are no direct benefits to you for participating in this research study. Serious risks, such as blood clots, are minimized by using transdermal (skin) estrogen patches and limited duration of exposure.

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary.

You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or

the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

Women in the menopause transition (meaning women who have irregular or skipped menstrual periods but have not gone a full year without a menstrual period) are more likely to suffer from depression and anxiety not only compared with men but also compared with women who still have regular menstrual periods (premenopausal women) and women who have not had a menstrual period in more than one year (postmenopausal women). The menopause transition is a time of extreme changes in sex hormone levels. One of the main female sex hormones is estrogen. Estrogen levels can change greatly from one day to the next during the menopause transition. In other research, changes in sex hormone levels have been shown to contribute to negative mood in women with severe premenstrual syndrome (PMS) and in women with postpartum depression. Estrogen has also been shown to influence brain areas that are important in the emergence of mood symptoms, including irritability. Although the causes of depression during the menopause transition are unknown, severe life stress close in time to the menopause transition is often associated with the onset of depression.

The purpose of this research study is to determine if changes in estrogen (specifically a urinary metabolite of estrogen, E1G) during the menopause transition are related to irritability symptoms and brain correlates of irritability, measured with electrodes on the scalp in response to computer tasks, the responses to which are correlated with anxiety and depression. We will also test whether administering estrogen for three weeks via a skin patch, will decrease irritability symptoms and beneficially modify brain circuitry associated with irritability symptoms.

What is known about hormone therapy, depression and health:

There are two general types of hormone therapy. Hormone therapy can involve either the use of estrogen alone (ERT; estrogen replacement therapy) or combined with another hormone called progesterone (HRT; estrogen plus a progesterone). For women who have not had a hysterectomy (still have a uterus), progesterone must be taken to prevent an overgrowth of cells in the uterine lining. There are several ways in which estrogen can be taken. It can be taken by mouth in the form of a pill, through the skin (in the form of a patch or a gel; this is called transdermal) or through a device placed in the uterus or vaginal ring. This study will use transdermal ERT (estrogen alone given through the skin) and oral progesterone given by mouth for 10 days at the end of your participation.

There have been a number of studies examining whether hormone therapy is effective in treating depression in women in the menopause transition or in postmenopausal women. While not all

studies have found that ERT or HRT is effective in treating depression, the majority of studies do indicate that ERT or HRT is linked to a large reduction in depressive symptoms in women in the menopause transition and in postmenopausal women.

There have also been studies in postmenopausal women suggesting that in women who used ERT or HRT during and/or after the menopause transition, their risk of heart disease was cut in half. However, in the Women's Health Initiative (WHI) study, that enrolled more than 27,000 women, the HRT part of the study was stopped after 5 years due to an increase in rates of breast cancer; the results also suggested an increase in non-fatal heart attack and stroke in women using the HRT.

Since then, reviews by the North American Menopause Society as well as other analyses, all conclude that the timing of HRT use has an impact on the benefits and risks associated with HRT. HRT or ERT appears to be beneficial or have no effects one way or another on heart health in women who start hormone therapy younger and closer to the menopause onset, and it appears to be harmful in women who are older or start hormone therapy a long time after onset of menopause. For example, later reports from the same Women's Health Initiative study have shown that women who were in their 50s and received ERT (estrogen alone) had a reduction in their chances of heart attack and stroke compared with women on placebo (an inert substance like a sugar pill).

In addition to timing, the preparation of hormones (i.e., whether estrogen is given alone or with progesterone and/or whether the hormones are taken by mouth or through the skin) is important in terms of both breast cancer and heart disease risk. For example, the reduced chance for heart attack and stroke seen in the younger aged women in the Women's Health Initiative was seen only in the women taking ERT (estrogen alone), not in those taking HRT (estrogen with a continuous progesterone). For breast cancer, prior studies suggest that ERT is associated with four times less of a chance of developing breast cancer than HRT. Also, the Women's Health Initiative results showed that only women who had a history of prior use of HRT (reflecting greater lifetime exposure to HRT) had an increased chance of developing breast cancer while there was no increase in chance of breast cancer in the women who had not used HRT prior to entering the study. Studies also indicate that duration of ERT or HRT use is an important factor in the chance for breast cancer.

In trying to estimate the chances of breast cancer associated with ERT, consider that in women 50-54 years of age not taking ERT or HRT, 13 out of every 1000 women will get breast cancer each year. In 50 – 54-year-old women who take ERT for 5 years or longer, 15 women out of every 1000 women will get breast cancer each year.

Other evidence that the preparation of hormones is important comes from evidence that use of transdermal estradiol (estradiol – the primary estrogen naturally produced in women - delivered through the skin), as we will do in this study, is associated with greater beneficial effects for a number of heart disease indicators than is the form of oral estrogen used in the Women's Health initiative (which was a modified horse estrogen). Transdermal estradiol is also more effective in treating depression than oral estrogen.

In summary, the Women's Health Initiative was not designed to examine the use of ERT in healthy women in the menopause transition – the group of women for whom there is a medically valid reason to use hormone replacement. For example, the Food and Drug Administration (FDA) has approved the use of estrogen to both treat menopausal symptoms (e.g., hot flushes, night sweats) and to prevent osteoporosis (bone loss) in women in the menopause transition.

The drugs used in this study (estrogen patch, progesterone) are approved by the FDA (as discussed previously) and are being used within that approval for this study.

You are being asked to be in the study because you are a healthy woman, 45 – 55 years of age, who is in the menopause transition defined by irregular periods.

Are there any reasons you should not be in this study?

You should not be in this study if you:

- have a history of heart disease, including coronary artery disease, arteriosclerosis, heart attack or stroke
- have high blood pressure that is not managed by medication (the researchers will measure your blood pressure)
- have a history of any estrogen-related cancer such as breast, ovarian, or uterine cancer or have a strong family history of estrogen-related cancer (the researchers will assess your personal and family history of cancer)
- have a history of thrombophlebitis or thromboembolic disorders (e.g., blood clots)
- are allergic to peanuts
- smoke more than 10 cigarettes per day
- have ever been diagnosed with bipolar disorder or a psychotic disorder
- are currently abusing or dependent on alcohol or drugs
- are currently taking antidepressant, antianxiety or other psychiatric medication
- have Type I diabetes
- use herbal supplements that are believed to affect mood or menopausal symptoms, such as St. John's Wort or black cohosh. If you use other herbal supplements, you should discuss them with the researchers who will determine if they are allowed
- have experienced migraine headaches with aura (aura means that you have a perceptual disturbance associated with the headache such as visual changes, a strange light, an unpleasant smell or confusing thoughts or experiences)
- have a Body Mass Index (BMI) of > 45 (this will be determined by the researchers)
- are pregnant or nursing

How many people will take part in this study?

Approximately 50 people at this institution will take part in this study.

How long will your part in this study last?

Your total participation will extend over approximately 16 weeks. There will be 1 in-person enrollment session, 3 in-person laboratory visits at a UNC site and will last approximately 1 hour, and the remainder of the study will take place remotely.

What will happen if you take part in the study?

1. Medical and Psychiatric Screening: The first phase of this study involves a phone screening for medical conditions, psychiatric history, and life events.

- You will then come into the lab to complete questionnaires or interviews about your medical history, your psychiatric history, your menstrual bleeding pattern, your mood, recent life events, your menopausal symptoms, and your sleep. You do not have to answer any questions that you do not want to.
- You will take a pregnancy test (urine test) to confirm that you are not pregnant before enrolling in the study.
- You will complete a psychiatric interview, during which you will be asked questions about your current and past mood symptoms. You do not have to answer any questions you do not want to. The interview may be audio recorded both for training purposes and for review to ensure a more accurate diagnosis of symptoms. We may refer to the audio recording to make diagnostic decisions after consulting with the study's clinician. Recordings will be stored with de-identified data on a HIPAA-compliant medical school drive for up to five (5) years after publication, at which point they will be deleted. If you are ineligible for the study, the recording will be deleted immediately. The audio recording is not required for participation. You may request that the audio recording be turned off.

  Please initial on the line that best matches your choice:

  _____ I AGREE to have my interview recorded

  _____ I DO NOT AGREE to have my interview recorded

2. Baseline hormone, mood and neurophysiological testing (4 weeks):

- Daily and weekly mood assessments:
  - Daily mood ratings using your personal cell phone: 10 questions on current mood and stress (~2 minutes to complete).
  - Weekly mood ratings on depression, irritability, and stress: 5-7 minutes to complete.
- Hormone fluctuations: Every-other-day urine collections (14 total): dried on collection card and placed in home freezer.
- Neurophysiological (EEG) testing session ~1 hour:
  - Electroencephalogram (EEG) recordings during:
    - rest (eyes open and fixated on cross, and eyes closed) – 5 minutes
    - emotional face task – 5 minutes

  - Two different computer tasks that are designed to assess behavioral indices of irritability. In one, you will look at pictures of faces and symbols and be asked to press a key in response to the symbols. This task lasts approximately 5 minutes. In the second task, you will be given a monetary award (up to $10 per laboratory session) depending on your performance.
- At the end of the baseline phase at the laboratory session, you will have the first patch placed. Each patch is good for one week. A study team member will visit you at your home to change your patch once per week and collect all used patches.
- You will be asked to wear your patch every day throughout both Condition 1 and Condition 2 (descried below). In one of the Conditions your patch will contain active estrogen (specifically 0.1 mg/day of estradiol) and in the other Condition your patch will be a placebo patch (containing an inert, non-active substance). Which Condition contains active estradiol versus placebo estradiol will be determined randomly (like flipping a coin). In other words, you have a 50-50 chance of Condition 1 being active estradiol or placebo and the same for Condition 2.

3. Condition 1 (3 weeks):

- Side effects, vitals and weight will be assessed at the end of each week in Condition 1 during the home visits to collect urine strips.
- Daily and weekly mood assessments:
  a. Daily mood ratings using your personal cell phone: 10 items (~2 minutes to complete) include questions on current mood and stress.
  b. Weekly mood ratings on depression, irritability, and stress: 5-7 minutes to complete.
  c. Daily urine collection during the last seven days of each Condition
- At the end of week 3 of Condition 1, you will return to the lab to complete the neurophysiological testing session (as described above)

4. Washout phase (3 weeks):

- During this phase you will not wear any patches.
- Side effects will be assessed by phone at the end of each week of the washout phase
- Daily and weekly mood assessments:
  - Daily mood ratings using your personal cell phone: 10 items (~2 minutes to complete) include questions on current mood and stress.
  - Weekly mood ratings on depression, irritability, and stress: 5-7 minutes to complete.

5. Condition 2 (3 weeks):

- You will be given a new patch which will be changed out weekly by a study team member (as described above).
- Side effects, vitals and weight will be assessed at the end of each week in Condition 2 during the home visits to collect urine strips.

- Daily and weekly mood assessments:
    a. Daily mood ratings using your personal cell phone: 10 items (~2 minutes to complete) include questions on current mood and stress.
    b. Weekly mood ratings on depression, irritability, and stress: 5-7 minutes to complete.
    c. Daily urine collection during the last week of the Condition
- At the end of week 3 of Condition 1, you will return to the lab to complete the neurophysiological testing session (as described above)

6. End of study and follow-up (3 weeks):

You will take two capsules per day for the last 10 days of the study, each containing 100 mg of micronized progesterone (total dose = 200 mg/day for 10 days). This is necessary to protect your endometrium (uterine lining) from getting too thick due to estradiol. The progesterone will induce menstrual bleeding, which it is designed to do, so that your uterine lining can shed. The number of days that of bleeding and the amount of bleeding varies between women. Because you are still having menstrual periods, it is anticipated that the amount of bleeding will not be more than your usual premenopausal bleeding, but this cannot be guaranteed.

You will complete weekly mood assessments, and side effects, vitals and weight will continue to be monitored.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. While the transdermal estradiol may have a positive benefit on mood symptoms, the possibility also exists that you will not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?
The **most common risks** involve side effects associated with the use of reproductive hormones (estradiol or progesterone).

The most frequent side effects associated with estradiol use include:

- breast tenderness (occurs in 29% of patients)
- abdominal cramps (occurs in 16% of patients)
- headache (occurs in 13% of patients)
- edema (swelling) (occurs in 10% of patients)
- nausea (occurs in 6% of patients)
- depression, nervousness (occurs in 11% of patients)
- acne (occurs in 3 – 12% of patients)
- skin rash or irritation may also occur at site where the patch is placed (occurs in 3 - 12% of patients)

Less frequent side effects include:

- jaundice (yellowing of skin)
- increased blood pressure
- worsening of migraines or asthma
- enlargement of uterine fibroids
- intolerance to contact lenses
- dizziness
- changes in appetite and weight

The most common side effects associated with progesterone include:

- breast tenderness (occurs in 16% of patients)
- dizziness (occurs in 24% of patients)
- abdominal cramping (occurs in 20% of patients)
- headache (occurs in 16% of patients)
- viral infection (occurs in 12% of patients)
- joint pain (occurs in 12% of patients)
- diarrhea (occurs in 8% of patients)
- menstrual bleeding, sometimes consistent with a heavy menstrual period (occurs in 20-30% of patients)
- drowsiness (occurs in 9% of patients)

Less common side effects include:

- vaginal discharge
- chest pain
- abdominal bloating

More Rare yet Serious Risks:

Venous Thromboembolism (blood clots) – the risk is increased with hormone use, but the risk is influenced by age and the preparation or type of hormone therapy. In the Women's Health Initiative Trial, the risk of venous thromboembolism in 50 – 59-year-old women taking estrogen replacement alone (without a daily progesterone) increased by less than 1% (that is, an additional 3-4 women out of every 1000 women taking estrogen replacement experienced a venous thromboembolism). The risk is even less with the use of transdermal estradiol.

Breast Cancer - ERT increases the risk of breast cancer but the risk is influenced by the duration of use. The risk in 50 – 54-year-old women who take estradiol alone for 5 years would increase from 13 out of every 1000 women not taking ERT (about 1%) to 14.94 per every 1000 women (about 1.5%).

Ovarian cancer – Long term use of ERT alone increases the risk of ovarian cancer, with a risk of 0.7 women per every 1000 women per every 5 years of use.

Endometrial Cancer - Exposure to estrogen by itself increases the risk of endometrial cancer two-fold (the endometrium is the lining of the uterus). However, use of a progesterone prevents the

increased risk of endometrial cancer. In the current research study, we plan to give a progesterone (200 mg/day) for 10 days at the end of your participation. In a prior study of Dr. Girdler's, that used the similar enrollment criteria as in this study (medically healthy women, 45 – 60 years of age in the menopause transition), progesterone was given at a dose of 200/mg day for 12 days every two or three months. Unlike this study, however, these women were treated with active estradiol (or placebo) for 12 months. Of the 86 women who received the active estrogen and this regimen of progesterone, one woman (1% of the women) developed endometrial hyperplasia which is a condition of excessive growth of the cells of the inner lining of the uterus. Endometrial hyperplasia is a risk factor for the development of endometrial cancer. However, in this case, the cells were not atypical, meaning that the cells were not characteristic of cancer cells. Because we are giving estradiol for only three weeks in the current study, the risk of developing endometrial hyperplasia, especially since you are still menstruating, is exceedingly low.

Stroke - It is possible that ERT increases the risk of stroke, but this is age dependent**.** ERT increased risk of stroke in the Women's Health Initiative study in 50 – 59-year-old women by an additional 1 case per 5000 women.

Risks Associated with Stopping the Hormones: There is a risk that stopping the hormones after the three weeks of estrogen or placebo will be associated with hot flashes, night sweats or vaginal dryness.

Minimizing these risks: The risk to you of these rare side effects are minimized as much as possible by the following: 1) your young age (45-55 years of age); 2) exposure to estradiol for only 3 weeks since short-term exposure (< 3 yrs.) has not been shown to be associated with an increased risk of breast cancer; 3) the use of micronized progesterone (200 mg/day for 10 days) in combination with the short exposure to estradiol and close monitoring of your bleeding patterns will substantially minimize the likelihood you develop endometrial hyperplasia and virtually eliminate any increased risk of endometrial cancer; 4) the frequent assessment of side effects; and 5) the provision of educational information so that you are fully aware of signs and symptoms that you should report to the study personnel.

Psychological Risks: The structured interviews to assess current and lifetime psychiatric illness may be associated with some psychological distress. Some items in the questionnaires may provoke some negative emotion in some individuals. There is also the risk you could experience the onset of a depression episode or have a worsening of depressive or anxious symptoms over the course of the study.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will information about you be protected?

No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Your privacy and confidentiality will be protected using ID numbers only and by securing all study files in a locked room. An electronic, password protected file linking your study ID number to you name and other identifying information will be kept separate from any study data. Only the researchers will have access to your identifiable information.

Your information and data collected for this research study will not be used or distributed for future research studies even if identifiers are removed.

What is a Certificate of Confidentiality?

This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers 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 proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Data sharing protection

Data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share deidentified information with each

other. A data repository is a large database where information from many studies is stored and managed. Deidentified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send deidentified information about your health and behavior to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You will not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

Please initial on the line that best matches your choice:

_____I AGREE to have research data entered into NDA and NIMH

_____I DO NOT AGREE to have research data entered into NDA and NIMH

If you agree to have research data entered into NDA and NIMH, please fill out the fields below, as they appear on your *most recent* birth certificate. This information will be used to generate the unique code number that will be associated with your data.

Name: First_____ Middle _____ Last _____

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. If you are hurt, become sick, or develop a reaction from something that was done as part of this study, the researcher will help you get medical care, but the University of North Carolina at Chapel Hill has not set aside funds to pay you for any such injuries, illnesses or reactions, or for the related medical care. Any costs for medical expenses will be billed to you or your insurance company. You may be responsible for any co-payments and your insurance may not cover the costs of study related injuries.

If you think you have been injured from taking part in this study, call the Principal Investigator at the phone number provided on this consent form. They will let you know what you should do.

By signing this form, you do not give up your right to seek payment or other rights if you are harmed as a result of being in this study.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

If you withdraw or are withdrawn from this study all data collected up until the point of withdrawal will be retained, however no additional information will be collected unless you provide additional written permission for further data collection at the time of your withdrawal.

Will you receive anything for being in this study?

You will be receiving up to $650 for taking part in this study. Any payment provided for participation in this study may be subject to applicable tax withholding obligations.

$25 for the enrollment session

$50 for each neurophysiological testing sessions ($150 total)
-Up to $10/session for task performance ($30 total)

$10/week for daily mood ratings ($130 total)

$5/week for survey collections ($80 total)

$35/week of urine collections ($210 total) *

$25 bonus for full compliance

*Please note that should the study team ask for additional urine samples beyond the 28 total allotted for the Baseline and two condition stages, you will be compensated $5 for each extra sample you provide. The additional compensation will be based on whether the study needs to follow up with you for additional collections. You cannot opt into it in order to obtain additional compensation.

Your name, phone number, address, and U.S. taxpayer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

U.S. person participants must complete Form W-9 in order to receive payment for participation. If payment by UNC equals or exceeds $600 per calendar year for U.S. persons, UNC will report the

amount to the Internal Revenue Service on Form 1099. Nonresident alien participants must complete Form W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents in order to receive payment for participation. Payments to nonresident alien participants may be subject to tax withholding and are generally reported to the Internal Revenue Service on Form 1042-S. This information will not be linked to any of the study data and will only be used for payment purposes.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?

It will not cost you anything to be in this study.

Who is sponsoring this study?

This research is funded by the National Institutes of Health. In addition, The Sabrina Nicole Hope Excellence Fund has gifted funds to purchase an EEG system for use in this study. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on 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 any time.

What if you have questions about your rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____
Signature of Research Participant

_____
Date

_____
Printed Name of Research Participant

_____
Signature of Research Team Member Obtaining Consent

_____
Date

_____
Printed Name of Research Team Member Obtaining Consent

_____
Signature of Witness if applicable (e.g. literacy issues, visually impaired, physically unable to sign, witness/interpreter for non-English speaking participants using the short form)

_____
Date

_____
Printed Name of Witness