Protocol Title

Cognitive Neuroscience of Reward v12.19.18

1) Principal Investigator

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IRB Review History

N/A

2) Objectives

The electroencephalographic response known as the Reward Positivity (RewP) is a promising candidate biomarker of diminished valuation in anhedonia. The RewP is only elicited by the presentation of a rewarding outcome and it scales with the central feature of reinforcement learning models, the *positive reward prediction error* (+RPE). Thus, the RewP is specific and sensitive to +RPE, fulfilling the stringent criteria of being an invariant neural marker of this computational process. Importantly, the RewP is boosted by appetitive states and is diminished in depressed individuals, indicating that emotional processes influence this marker of reward learning. While prior work has effectively described these correlations (e.g. Foti and Hajcak, 2009), we do not know how emotion (e.g. depression) and +RPE interact to influence valuation. The objective of this proposal is to test whether mood directly diminishes +RPE coding in the RewP, or if these are separable influences on this signal.

Aim 1: To determine if affect and +RPE have independent or interactive effects on the RewP. Based on our working hypothesis, a sadness manipulation in healthy controls should diminish the RewP. Computational modeling will identify the parameters best associated with the influence of affect on learning, allowing us to capture the richness of these effects in an objective and consistent manner. Statistical modeling will quantify the independent vs. interactive influences of affective and +RPE processes on both the RewP and reward learning.

Aim 2: To determine if anhedonia and +RPE have independent or interactive influences on the source-level generators underlying the RewP. We will use gold-standard source-estimation techniques including concurrent EEG and MEG with MRI-based structural templates and an fMRI-based reward-localizer mask. These tools will be integrated to test our working hypothesis that anhedonia-specific reductions in the M/EEG RewP in depression will co-localize with +RPE in subgenual and ventromedial frontal cortex. This finding will identify a common mechanism for anhedonia-based reductions in reward responsivity.

3) Background

The RewP is enhanced with positive affective manipulations (Brown & Cavanagh, 2018; Threadgill & Gable, 2017) and it scales with self-reported and behavioral reward responsiveness (Bress, Smith, Foti, Klein, & Hajcak, 2012). The RewP is diminished in depressed individuals (Bress et al., 2012; Foti & Hajcak, 2009), particularly a melancholic subtype closely related to anhedonia (Foti, Carlson, Sauder, & Proudfit, 2014; Liu et al., 2014). A reduced RewP is observed in children most vulnerable to depression (Kujawa, Proudfit, & Klein, 2014), and it can predict the probability of a future major depressive episode in never-depressed individuals (Bress, Foti, Kotov, Klein, & Hajcak, 2013). The RewP is has good test-retest reliability (Kujawa et al., 2017; Levinson, Speed, Infantolino, & Hajcak, 2017) and internal reliability (Bress, Meyer, & Proudfit, 2015), including reliable diminution due to depressive symptoms (Bress et al., 2015). In sum, these findings demonstrate that the RewP has the sensitivity, specificity, validity, reliability, and prognostic value desired in a biomarker.

However, there is no formal model of the joint sensitivity of the RewP to emotion and +RPE signaling, and thus there is no explanation for the diminishment of this signal in depression. The core problem is that we do not know if emotion influences +RPE coding via the RewP. The statistical interaction of depressed mood and poorer +RPE encoding would identify the RewP as a mechanism of diminished valuation in anhedonia. Conversely, if these are independent influences on the RewP (i.e. main effects), then diminished valuation is likely to be encoded in the downstream targets of the generative area (likely striatum).

The current proposal addresses this hypothesis in separate aims that will manipulate this expression in healthy controls and assess these natural features in anhedonic depressed individuals. This contribution is expected to be significant because it will advance a translational mechanism for deficient valuation in anhedonia.

4) Inclusion and Exclusion Criteria

Inclusion criteria:

- Men or women aged 18-55
- In Aim 2, participants will need to either meet criteria for Major Depressive Disorder via a Structured Clinical Interview for the DSM-5 (SCID), or have an absence of symptoms to qualify as a control.
- Free from psychoactive medication for at least 2 weeks

Exclusion criteria:

- Participants unwilling or unable to give informed consent
- Presence of other known medical or psychiatric comorbidity that in the investigator's opinion would compromise participation in the study
- For Aim 2, MEG/MRI contraindications
- Any other Axis 1 disorder (unless secondary to depression for depressed group in Aim 2)
- History of psychosis
- Not fluent in English

5) Multi-Site Research

N/A

6) Study Timelines

For Aim 1, individual participant's involvement will last 2-3 hours during 1 day. For Aim 2, individual participant's involvement will last 4-7 hours over 1-2 days. Both aims have a longitudinal component where we will perform a phone interview 3-6 months after the initial assessment. This phone interview consists of a Beck Depression Inventory and is described more in detail in Section 9. We anticipate ongoing enrollment of participants for five years.

7) Study Endpoints

N/A

8) Study Methods

Participants will be asked to complete the following procedures:

Magnetic Resonance Imaging (MRI) scan(s) that may or may not involve simultaneous functional or cognitive tasks. Participants will lie down on a table and be placed into a long donut-shaped magnet. During the scan, participants may be shown pictures and/or words and will be asked to make decisions about the information presented in them. This takes about 1 hour.

Electroencephalograph (EEG) may be done at the same time as the MRI or MEG scan. If so, the participant will wear a cap during the MRI/MEG to record brain waves. Alternatively, the EEG may be performed separately. This takes about 2 hours.

Magnetoencephalography (MEG) records the magnetic activity of the brain at rest and while a person works on a set of tasks. It is performed while sitting in a comfortable chair in a special, magnetically shielded room. MEG does not emit radiation or magnetic fields. Electrodes will be applied to the participant's head and face using a special conductive gel. These will be held in place with a cap or sticky tape. These electrodes are used to monitor brain activity, eye movements, head position, and heartbeat. When the scan is over, all of the electrodes will be removed. This takes about 1 hour of assessment and up to 1 hour of setup.

Neurocognitive testing: In order to examine specific cognitive mechanisms that may be associated with neuropsychiatric disorders, participants will be asked to complete tasks (e.g. remembering letters or numbers, deciding between different monetary options) for up to 2 hours of total testing.

Participants will be asked to complete one or more of the following questionnaires:

- Demographics (age, gender, race, contact and alternate contact information, etc.)
- Handedness questionnaire
- Beck Depression Inventory (BDI)
- Mood and Anxiety Symptoms Questionniare (MASQ)
- Behavioral Inhibition / Activation Scales (BIS/BAS)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Dimensional Anhedonia Rating Scale (DARS)
- Apathy-Motivation Index (AMI)
- Diagnosis information (SCID)

They may refuse to answer any question at any time. These questionnaires may take 2 hours to complete. Direct identifiers will be collected and maintained in the MRN COINS database. All data collected as part of this study will be coded with a Unique Research Subject Identifier (URSI).

Tasks: All tasks are NIMH Research Domain Criteria (RDoC) paradigms that have been previously utilized in studies of depression.

1) The Probabilistic Stimulus Selection task (Frank, Seeberger, & O'Reilly R, 2004) will be identical to the PI's previous work (Cavanagh et al., 2010a, 2010b, 2011a, 2011b, 2014). The sophistication of the three separately valued training pairs facilitates a wide range of +RPE values and assessments of reward vs. punishment learning. During training, participants slowly learn to select the optimal item in each pair based solely on probabilistic reinforcement rates. EEG locked to the reinforcing feedback ("correct") elicits the RewP.

2) The Probabilistic Rewards task (Pizzagalli, Jahn, & O'Shea, 2005) will be used to assess a commonly-observed decrement in reward learning in depression (Bogdan & Pizzagalli, 2006; Pizzagalli et al., 2005; Vrieze et al., 2013).

3) The Gambling task (Foti & Hajcak, 2009) is an extremely rapid assessment (~5 minutes) of neural responses to reward and punishment.

4) The Effort Expenditure for Rewards Task (EEfRT: Treadway et al., 2009, 2013) measures a participant's willingness to press buttons over time in order to get reward.

Aim 1 will assess tasks 1,2, and 3 with EEG. Aim 2 will assess task 1 and 2 with MEG and concurrent EEG, task 3 with fMRI, and the 4th task will only be assessed as a behavioral task (no imaging).

Mood and Emotion Manipulations: Mood and emotion manipulation procedures will only be used in Aim 1 (EEG in Logan Hall) and not in Aim 2 (EEG, MEG, and MRI at the MRN). Mood maniupulation will occur during EEG assessment, immediately prior to task performance.

In Aim 1a, a mood induction procedure will be utilized in control (non-depressed participants only), similar to Mayberg et al. (1999b), based on the suggestions of Martin (1990). The procedure consists of a combination of re-experiencing an autobiographical sad personal event while listening to their choice of one of four sad music selections commonly used in mood induction (Ramel et al., 2007). Visual analgoue scale ratings will assess momentary sadness prior to, following, and at subsequent time points around the mood induction procedure. A positive mood repair procedure will be used after the tasks in order to ensure that the participant experiences the sadness experience as transitory.

In **Aim 1b**, emotional images similar to positive and negative International Affective Picture Set (IAPS: Bradley & Lang, 1999) images or emotional faces (Ekman, 1992) will be used to alter the emotional information of stimuli or reinforcements. Aim 1b will contain both control and depressed participants.

The three-to-six month followup phone interview will consist of a verbal or online (via COINS) completion of a Beck Depression Inventory. If participants consent to a follow-up phone interview, they will be contacted by research staff and asked if they are still interested in completing the survey. If they agree, a time and method for completion (verbal or online) will be setup. It should take 5-12 minutes to complete the BDI.

9) List of Appendices

Demographics form (age, gender, race, etc.)
Handedness questionnaire
Beck Depression Inventory (BDI)
Diagnosis information (SCID)
Mood and Anxiety Symptoms Questionniare (MASQ)
Behavioral Inhibition / Activation Scales (BIS/BAS)
Snaith-Hamilton Pleasure Scale (SHAPS)
Dimensional Anhedonia Rating Scale (DARS)
Apathy-Motivation Index (AMI)

10) Data and Specimen Banking

No specimens will be banked as part of this protocol. Participants will be given the option of having their data stored in the MRN Data Repository (see HRRC# 06-387, PI: Roberts).

11) Data Management

Consent Forms/HIPAA Authorizations: Signed consent forms are stored in a locked cabinet in a locked office in Logan hall on UNM main campus.

Questionnaire Data: All data are coded with a unique research subject identifier (URSI) number. Electronic data is stored on a drive only accessible by the research team on a secure server. For non-computer based forms, such as the neuropsychological assessments, the data collection sheets are stored in a locked cabinet in a locked office in Logan hall on UNM main campus.

Behavioral and Imaging Data: All data is coded with the URSI, and collected and stored electronically. Electronic data is stored on a drive only accessible by the research team on a secure MRN server. De-identified data resulting from this study may also be presented at meetings, published in journals/books, used in classrooms for training/teaching purposes, and may be shared with other researchers including scientists at other universities and institutions. De-identified information from this study will be submitted to online data repositories including the Patient Repository for EEG Data + Computational Tools (www.predictsite.com) and the National Instituties of Mental Health Research Domain Criteria database (www.rdocdb.com) .

Study Closure: At the time of study closure, all participant identifiers (name, address, etc.) will be made inaccessible to the research team. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that may be present in radiological scans and reviews. For example, if a participant has been diagnosed with a neurological condition (e.g., multiple sclerosis, glioblastoma, etc.) it may be clinically beneficial for the participant's physician to have access to a research scan that was performed at an earlier time-point to determine disease course and severity.

Statistical Analysis: All data will undergo standard preprocessing (e.g. motion correction, spatial normalization) and quality control prior to statistical modeling. Depending on the specific question of the study, data may be analyzed using the general linear model, independent components analysis, machine learning techniques, or a variety of other standard approaches for neuroimaging data.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects

This study is minimal risk. Any reportable events will be submitted to the OIRB within 7 days

13) Participant Complaints

If a participant wishes to issue a compliant or request information about the research, they may notify any study team member or the PI, James F. Cavanagh, at (505) 277-6830, Monday-Friday from 9am-5pm). Participants may also contact the UNM Office of the IRB, (505) 277-2644, irbmaincampus@unm.edu. Website: http://irb.unm.edu/

Depending on the nature of the complaint, the problem will be resolved directly with the participant, if possible, in a confidential and timely manner. Complaints that constitute a reportable event will be submitted to the IRB within 7 days. Participant complaints will be coded with a unique research subject identifier (URSI) and kept in their respective study folder in a locked office for record-keeping purposes.

14) Withdrawal of Subjects

Participants may withdraw from the study at any time.

The investigators may end an individual's participation in the study if the participant is no longer eligible, if the participant does not follow study procedures (e.g. sleeping in the MRI, not completing assessments, etc.), or if they decide that it is in the participant's best interest, or the study's best interest to stop participation.

15) Risks to Subjects

MRI: Radio and magnetic waves associated with MRI scans are not associated with any known adverse effects. MRI is non-invasive and considered minimal risk by the FDA and OHRP. However, the scanner is a large magnet, so it could move objects containing ferrous metal in the room during the scan. All participants are screened using the MRI safety screening form prior to be being scanned. Participants may be bothered by feelings of claustrophobia (uncommon). The MRI also makes loud 'drum' beating noises during the study. Headphones or earplugs are provided for protection. Rarely, large or recent tattoos can heat up during an MRI scan and cause skin irritation like a sunburn (uncommon). No long-term harmful effects from MRI are known. However, since the effect of MRI on early development of the fetus is unknown, participants who are pregnant will not be allowed to go in the MRI. Females who have had their first menstrual period, and who suspect they may be pregnant, will be asked to take a urine pregnancy test before being allowed to participate in the study. The test results will only be shared with participant. All MRI sequences used are within FDA approved parameters, including specific absorption rate. Due to the very high sensitivity of MRI in detecting abnormalities, there is a risk of false-positive findings, identifying something on imaging studies that may or may not be important. This may result in anxiety and a referral for additional medical testing, possibly including a recommendation for clinical scans at the participant's cost.

EEG/MEG: There is a very small possibility that participants with sensitive skin (e.g., contact dermatitis) may experience some skin irritation from the EEG gel or metal sensor (uncommon).

A safety monitoring play will be followed to protect against intent for self-harm. All questionnaire scales will be immediately (within 1 day) examined for endorsement of suicidal ideation. If the participant endorses suicidal ideation (scoring 2 or 3 on item #9 of the Beck Depression Inventory) the PI will be immediately notified. The participant will then be contacted in person or over the phone by a senior member of the research team. Initially, the PI will lead all phone contacts and will use these as training experiences for other senior members of the research team (PhD student or post-doc level). The PI has extensive experience with these phone screening procedures: he was in a mood and anxiety disorders laboratory during PhD training at the University of Arizona and was trained by the clinical psychologist PI on these procedures for his multi-year dissertation work on major depression. This phone screen protocol consists of multiple steps to protect participant confidentiality:

1) The experimenter will verify via person-to-person contact with the participant that this is a "*good time to talk discretely*" prior to raising the reason for the call about the depression rating score for suicidality.
2) If the participant endorses thoughts of suicidality they will be notified of number of local counseling and psychiatric resources, including 24 hour hotlines and free or low cost counseling services. A list of these resources has been attached to this submission.
3) If the participant endorses imminent suicidal ideation, the PI will call 911 to inform emergency responders of the participant's location and imminent suicide plans. Note that this is likely to be very rare.

There are risks of loss of privacy, getting insured, being employed, and stigmatization.

General (uncommon) risks: Participation in this study may result in discomfort, emotional stress, behavioral fatigue, and inconvenience.

Privacy and Confidentiality: Participation in this study may produce emotional stress, inconvenience or an invasion of privacy (uncommon). There is also a risk of breach of data confidentiality (uncommon).

There may also be side effects or risks to study participation that are unforeseen and not known at this time.

16) Potential Benefits to Subjects

Participants will receive a radiologist's review and report of their MRI scan and will be compensated for their time and inconvenience. No other direct benefit to participants is anticipated.

17) Compensation of Subjects

Participants will be compensated $20/hour (Aim 1) or $30/hour (Aim 2) in cash or gift card for participating in this study. Some tasks may have a monetary reward component which will allow the participant to earn between $2 and $20 extra depending on task performance. Participants will be paid in person (or mailed) at the completion of each study visit. This is a typical method and rate by which participants are compensated for their time, inconvenience and travel expenses.

18) Vulnerable Populations

There will be no vulnerable populations in this study (only consenting adults).

19) Community-Based Participatory Research/Field Research

N/A

20) Sharing of Results with Subjects/Incidental Findings

All research MRI scans are read for incidental findings by a radiologist unless the individual has been scanned at MRN in the previous six months. If the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the COINS Homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the MRN Medical Director may also attempt to contact the participant by phone to explain the information and help answer questions.

21) Research Setting

All study procedures will take place at the Mind Research Network or in the PI's lab in Logan hall.

22) Resources Available

The PI and study team are all experienced neuroimaging researchers. John Phillips serves as MRN Medical Director. Located on UNM's north campus, MRN is a 501(c)3 non-profit organization consisting of an interdisciplinary association of scientists focused on state-of-the-art imaging technology and its emergence as an integral element of neuroscience investigation.

On UNM main campus, the PI has a dedicated lab space with two testing booths and access to four more testing booths in the Psychology Clinical Neuroscience Center. EEG systems are available for use in two of these testing rooms. Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. The imaging facilities at the MRN also have private changing rooms with lockers for personal items. All research staff are trained in regards to the HIPAA Privacy Rule. All individuals will be trained to administer the same consenting and study procedures. Further, all study personnel will have current CITI and HIPAA training throughout the period of the study.

23) Prior Approvals/Attachments Requiring Signatures

Just-in-time request fulfills requirement of prior departmental approval.

24) Recruitment Methods

1.1 Depressed participants will be recruited from UNM Psychiatric Center and the UNM primary care behavioral health clinics (via Co-I Quinn), announcements for referral on the New Mexico Psychological Association and State Psychological Association listservs, and community advertisements.

1.2 Participants will be recruited from the methods detailed in the bullet points below.

1.3 Methods for recruitment are detailed in the bullet points below.

1.4 Flier and Online recruitment scripts are attached

Participants in this study may be recruited by:

- Depressed participants will be given the flier with contact information. They will also be asked if they consent to be contacted by the study team. If so, the name and phone number will be emailed to the research team using password-protected email.
- Posting/handing out/e-mailing IRB approved materials in locations where the general public gathers/there are bulletin boards available for posting/community agencies that serve the general public throughout Albuquerque and the surrounding areas. Where possible and appropriate, permission will be sought from managers/site directors prior to materials being posted.
- Word of mouth from current and past participants, employees and collaborators, as well as other individuals will also be used and may include sharing approved information and/or recruitment materials.
- On-line and mobile-based postings through websites and apps such as the MRN website, Craigslist, Google Adwords, as well as email distribution groups and listservs.

25) Local Number of Subjects

For Aim 1, we anticipant enrolling N=50 depressed participants and N=150 control participants. For Aim 2, we anticipate enrolling N=50 depressed participants and N=50 control participants. The total N for enrollment will be 300.

26) Confidentiality

All participants are assigned a study ID (URSI) that links their data with their name and other identifying information. All study data (with the exception of the consent form and payment receipt) are coded only with this number. The information is maintained in a secure, restricted

access database. After completion of data analysis, the linking code will be made inaccessible to the research team. De-identified data will be retained until data analysis activities are complete.

In addition to the above protections, this study has a Certificate of Confidentiality from NIH to further protect participant confidentiality. Importantly, as stated in the consent, participants are informed that if they report current abuse of a child or an elder, we will report the person to the proper authorities, consistent with New Mexico state law.

27) Provisions to Protect the Privacy of Subjects

On UNM main campus, all private testing rooms are located in a locked testing facility on the 2nd floor of Logan hall. Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. The imaging facilities also have private changing rooms with lockers for personal items.

28) Compensation for Research-Related Injury

No commitment is made by the MRN or UNM to provide free medical care or money for injuries to participants in this study. This is clearly stated in the consent form.

29) Economic Burden to Subjects

Participants will not be charged for any of the experimental study procedures, including MRI scans. If incidental findings from the study result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information also to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

30) Consent Process

Upon initial contact, the study will be briefly introduced to the participant by a member of the research team. Participants will then be screened over the phone or in person. Identifiable information will be neither recorded nor retained for those participants who do not meet inclusion criteria. If the participant meets inclusion criteria, the study visit will be scheduled and an informational brochure and copy of the consent document will be sent to them if requested. When the participant arrives for their appointment, the participant will be seated in a private room and given time to read the consent form. After the participant has finished reading the consent form, the study is described more fully by the research team and the participant is asked whether they have any questions regarding the described procedures and risks/benefits. Participants must elect to participate and can choose to discontinue their participation in the study at any time. If requested, we will show the participants the equipment that will be used to perform the study. In addition, we may ask some basic questions of the participants about the proposed study to ensure that the participants understand the nature of the experiment. No coercion or undue influence will be used.

If there are no further questions, the consent form is signed and stored in a locked cabinet in a locked office in Logan Hall on UNM main campus. A copy will be given to the participant.

31) Drugs or Devices

N/A

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