TITLE: Causal Dissociation of Value Contributions to the Reward Positivity

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BACKGROUND/SCIENTIFIC RATIONALE

The aim of this proposal is to demonstrate that stimulation of different brain regions differently affects the electroencephalographic (EEG) feature known as the Reward Positivity (RewP). The RewP is a sensitive and specific biomarker of reward receipt occurring 200-350 ms after presentation of the rewarding image. The RewP appears as a positive going voltage deflection over mid-frontal scalp sites, and can be elicited by any feedback indicating a rewarding outcome (e.g. "correct", thumbs-up emoji, +$, etc). Two factors modulate the RewP: 1) the degree of reward surprise (the Reward Prediction Error) and 2) affective influences like "liking" the stimulus (e.g. a picture of a cute puppy instead of a thumbs-up emoji). These two factors appear to account for separate variance in the RewP.

Our *long-term goal* is to validate the RewP as a bench-to-bedside electrophysiological biomarker of reward processing. The RewP is has good test-retest reliability (Kujawa et al. 2017; Levinson et al. 2017) and internal reliability (Bress et al. 2015). The RewP also has reliable diminution due to depressive symptoms (Bress et al. 2015) and it predicts cognitive behavioral therapy responsivity in depression (Burkhouse et al. 2016). These psychometric strengths compliment the aforementioned specificity to reward and sensitivity to multiple aspects of valuation. In sum, *the RewP has the sensitivity, specificity, validity, reliability, and prognostic value desired in a biomarker*.

This proposal will advance a causal test of the hypothesis that there are two major sources of variance that contribute to this brain response: a dorsomedial cortical contribution to information encoding (Cavanagh 2015; Frömer et al. 2016) and a ventromedial cortical contribution that is modulated by affect (Foti and Hajcak 2009; Threadgill and Gable 2017). Together, these findings will reveal how the RewP acts to blend multiple aspects of value together in the service of motivated learning, and demonstrate why this signal is a compelling mechanistic biomarker of anhedonia. Motivated by these prior EEG sensor-level findings, our current ongoing magnetoencephalography (MEG) work has successfully verified these different source-level influences during the time of the RewP.

The RewP holds promise as a surrogate endpoint in Phase I/II clinical trials (Fleming and DeMets 1996) for individualized assessment of treatment response in depression (see: Burkhouse et al., 2016). However, a systems-level causal manipulation is required in both species before we advance these translational aims. The *objective* of this proposal is to gather pilot data to demonstrate the feasibility of using transcranial magnetic stimulation (TMS) to perturb idiosyncratically-defined (fMRI-based) dorsal or ventral cortical targets in order to causally test the hypothesis that these different sources contribute different types of variance to the RewP. TMS offers the best opportunity for system-specific alteration of the source-level generators of the RewP. The use of fMRI to identify individualized targets has emerged as the gold-standard for TMS targeting of specific neural systems (Sack et al. 2009; Parkin et al. 2015). For the purpose of this proposal, we will test a between-subjects double-dissociated hypothesis of separate source computations to the EEG and MEG features of the RewP, predicated on individualized fMRI localization of TMS targets

OBJECTIVES/AIMS

Participants will be recruited from the Albuquerque community. Each participant will first undergo a reinforcement learning task in fMRI. Individualized stimulation targets will be identified based on the task and rest fMRI; participants will then be randomly assigned to either Aim 1 or Aim 2.

Each participant will receive active and sham stimulation, with sessions taking place ≥1 week apart. Post-TMS assessment will utilize MEG with an EEG lead at the vertex for simultaneous assessment of the formally-defined EEG-based RewP component. In these MEG assessments, we will use counterbalanced variants of a recently developed affective value-based reinforcement learning task developed in our lab (Brown et al. 2021), which will allow us to assess the orthogonal influence of Reward Prediction Error vs. affective value on the RewP.

Aim 1: To stimulate fMRI-informed *individualized targets* in anterior midcingulate cortex to diminish Reward Prediction Error encoding in the RewP. Based on our *working hypothesis*, TMS double cone deep coil stimulation should diminish Reward Prediction Error encoding in the RewP (via EEG) and in anterior midcingulate areas (via MEG) when compared to sham.

Aim 2: To stimulate fMRI-informed *individualized targets* in dorsolateral prefrontal cortex to diminish affective modulation of the RewP. Based on our *working hypothesis*, TMS Figure-8 coil stimulation should diminish affective modulation of RewP amplitude (via EEG) and in ventromedial prefrontal cortex (via MEG) when compared to sham.

PROJECT DESIGN

I. *Target Population and Inclusion/Exclusion Criteria*

Inclusion criteria:

- Men or women aged 18-55
- Fluent in English
- Free from psychoactive medication for at least 2 weeks
- Beck Depression Inventory score <12

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 (e.g. claustrophobia, psychosis)
- MEG/MRI contraindications (see MRI screening form)
- TMS contraindications (see TMS screening form)

II. *Participant Enrollment*

Since this current project is funded as a pilot feasibility study, we will enroll only up to 12 participants.

III. *Recruitment and Screening Procedures*

Participants in this study may be recruited by:

- 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.

IV. *Informed 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, including MRI and TMS safety screening. Identifiable information will be neither recorded nor retained for those participants who do not meet inclusion criteria. If the participant meets inclusion and exclusion 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.

V. *Data Collection Procedures*

Participants recruited for the study will be invited to complete three experimental sessions as soon as it is convenient for them to come in. The first session will be 2 hours, and the next two sessions will be up to 3 hours each over a period of approximately 1 week

- The first experimental session will include consent and questionnaires (1 hour), plus one MRI scan of functional task performance (1 hour).
- The second and third sessions will include MEG/EEG setup (<1 hour), TMS (1 hour), and MEG/EEG assessment (1 hour). The TMS target will be derived from the peak fMRI signal from the first session. The difference between the second and third days will solely be in the randomized application of active or sham stimulation (see below).

Magnetic Resonance Imaging (MRI) scan(s) will involve a functional / cognitive task. Participants will lie down on a table and be placed into a long donut-shaped magnet. During the scan, participants will complete the task described below. This takes under 1 hour.

Electroencephalograph (EEG) will be done at the same time as the MRI or MEG scan. The participant will wear a cap during the MRI/MEG to record brain waves. Alternatively, the EEG may be performed separately. This takes up to 1 hour of setup and 1 hour of scanning.

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. During the scan, participants will complete the task described below. When the scan is over, all of the electrodes will be removed. This takes up to 1 hour of setup and 1 hour of scanning.

Questionnaires: Participants will be asked to complete the following questionnaires:

- Demographics (age, gender, race, contact and alternate contact information, etc.)
- Handedness questionnaire
- Beck Depression Inventory (BDI)
- Behavioral Inhibition / Activation Scales (BIS/BAS)

Participants may refuse to answer any question at any time. These questionnaires may take up to 1 hour 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 have been previously utilized in the PI's work:

1) The reinforcement learning task used as the fMRI task will be similar to the PI's previous work (Cavanagh et al., 2010a, 2010b, 2011a, 2011b, 2014). Three stimuli will appear on the screen; each has a varied, time-dependent reinforcement probability for stimulus-action decisions (e.g. yellow triangle rewards a left button push 70% of the time, blue square rewards a right button push 80% of the time, etc.). The sophistication of the three separately reinforced stimuli facilitates a wide range of Reward Prediction Error values.

2) The affective state reinforcement learning task will be used as the MEG/EEG assessment task. This task was recently developed in the PI's lab (Brown et al., 2021). It is a general reinforcement learning task with a cross-over design: each separate imperative stimulus is associated with a reward probability (high vs low Reward Prediction Error, e.g. 65% correct or 80% correct feedback) as well as an affective image presented at feedback (preferred vs. less preferred image: e.g. puppies vs. cows). This design allows a cross-over decomposition of reward surprise vs. affective 'liking'. Prior to the first affective state task, participants will rate images (1-9 scale) of puppies, babies, scenery, cows, lightbulbs, and unpleasant images as a face-valid verification of 'liking' of image classes (as in Brown et al., 2021).

TMS: The following devices will be used in the study: a Magventure MagPro X100 (Magventure, Inc., Alpharette, Georgia, USA). This TMS device is FDA approved for the treatment of treatment-resistant depression. The TMS device used in this study is determined to be a Non-Significant Risk device by the Principal Investigator. The device is housed at UNM in the Noninvasive Neurostimulation Lab in Dominici Hall, and access will be limited to study personnel who are trained to use this device safely.

TMS Protocol: On day 2 or 3 of the protocol (randomized), single pulses of TMS will be applied over the scalp area overlying the participants' motor cortex using a handheld TMS coil. TMS pulses will be delivered through an air-cooled coil in either a figure-eight or double-cone shape, with the latter being particularly useful for targeting deeper structures such as midcingulate cortex. The first phase of the TMS protocol will involve a standardized motor-thresholding procedure, wherein peripheral responses evoked by single TMS pulses (100% of the motor threshold) are recorded via an electromyographic recording device (BIOPAC Systems, Inc., Goleta, CA). In this phase, the TMS coil's stimulation intensity is titrated to a level that is comfortable yet effective at reliably exciting neuronal populations orthogonal to the coil (50% MEPs ≥50μv; typical duration≈20-40 mins). Then, the repetitive TMS (rTMS) procedure will be administered to a pre-determined cortical target based on the individual's pre-TMS fMRI scan using a Localite Neuronavigation system (TMS Navigator, Localite GmbH, Bonn, Germany; duration≈10-20 mins). The rTMS protocol will involve the delivery of a train of TMS pulses over a cortical target prior to performance of the behavioral tasks during a post-rTMS fMRI scan. Sham procedures will be identical, but will involve the delivery of subtle electrical stimulation underneath the TMS coil to mimic the tactile effects of rTMS *without* delivery of neuromagnetic stimulation.

Both single pulse TMS / motor thresholding and rTMS are extremely safe when used within the safety guidelines for TMS. As an additional precaution, participants will be screened for contraindications to TMS using a gold standard questionnaire. Our TMS protocol will involve one of two safe and widely used 'theta-burst' stimulation procedures, which are used to drastically reduce the total amount of time required for rTMS pulse delivery (Huang et al., 2005). Theta burst rTMS will take the form of either *intermittent* theta burst stimulation (up to 1200 pulses delivered in 50Hz triplets for 2s every 10s with an 8s gap, resulting in a total stimulation duration of 190s) or *continuous* theta burst stimulation (up to 3600 pulses delivered in 50Hz triplets continuously for 40s). Intermitted theta burst enhances cortical excitability at the target site, whereas continuous theta burst stimulation inhibits cortical excitability. However, prior studies have observed conflicting beneficial cognitive effects of both excitatory (e.g. Wang et al., 2014) and inhibitory (e.g. Tambini et al., 2018). Since this is a pilot study, we will evaluate the behavioral and neural connectivity data throughout data collection. If the effects are not trending in the hypothesized direction we will plan to reevaluate and potential shift to a continuous theta burst protocol.

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), as well as other open-source repositories (PRED+CT, Openneuro.org, etc).

VI. *Anticipated End Date*

The end date will be the conclusion of the pilot funding period: 05/31/2023 or after 12 participants have completed the study, whichever is later.

VII. *Project Location(s)*

All study procedures will take place in Dominici Hall, including the Mind Research Network, or in the PI's lab in Logan hall.

VIII. *Participant Compensation*

Participants will be compensated $25/hour in cash or gift cards for participating in this study. Participants will be paid in person at the completion of each study visit, any incomplete visits will be prorated according to the time of participation. Since this project includes three separate visits, a $50 bonus will be awarded at the end of the completed third visit. This is a typical method and rate by which participants are compensated for their time, inconvenience and travel expenses. Total compensation per participant is expected to be:

- Session 1: 2 hours @ $25 / hr = $50
- Session 2: 3 hours @ $25 / hr = $75
- Session 3: 3 hours @ $25 / hr = $75 + $50 bonus
- Total compensation: $50 + $75 + $75 + $50 = $250

IX. *Project Resources*

The PI and study team are all experienced neuroimaging researchers. 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. John Phillips serves as MRN Medical Director.

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. 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.

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.

EXPECTED RISKS/BENEFITS

I. *Potential Risks*

There are risks of loss of privacy and stigmatization.

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).

TMS: TMS is considered a minimal risk procedure but can produce side effects that are noted here. Most people do not find TMS painful but occasionally strong contractions of the scalp muscles can cause discomfort or headache that usually go away promptly with nonprescription medication. The noise of the TMS magnet may affect hearing, so participants will be fitted with earplugs. Like MRI, TMS involves the use of a powerful magnet. Thus TMS will not be performed on people who have pacemakers, implanted pumps or stimulators, or who have metal objects inside their heads. The risk of inducing seizure with TMS is considered very low at <0.1%. However, certain factors increase the risk of seizure such as sleep deprivation, family history of seizures, polypharmacy, alcohol use, and previous neurological conditions. Participants will be carefully screened for these factors to ensure that risk of seizure is minimized.

General (uncommon) risks: Participation in this study may result in discomfort, emotional stress, behavioral fatigue, and inconvenience. All pictures used in the emotion task itself are positively valenced or neutral pictures (e.g. puppies, cows, lightbulbs, chairs) except for the pre-task image rating procedure, which includes five negatively valenced pictures. However, these pictures were chosen specifically to minimize negative impact (graveyard, cigarette butts, garbage on sidewalk), so we do not anticipate any emotional stress to be due to the affective images used in this study.

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.

II. *Benefits*

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. This work is part of a larger research program to identify the RewP as a potential mechanistic marker of anhedonic depression, which will advance novel diagnostic and treatment targets.

III. *Privacy of Participants*

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. On UNM main campus, all private testing rooms are located in a locked testing facility on the 2nd floor of Logan hall.

IV. *Unanticipated Problems/Adverse Events*

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.

All depression rating form entries will be discreetly examined during the experimental session for endorsement of suicidal ideation (score of 2 or 3 on BDI item #9). Please see the BDI Safety Monitoring Plan document for the lab protocol for managing this potential unanticipated problem.

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.

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.

V. *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/

PROJECT DATA

I. *Data Management Procedures and Confidentiality*

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 and/or in the COINS database on a secure HIPAA compliant cloud based server. For non-computer based forms, such as the questionnaire assessments, the data collection sheets are stored in a locked cabinet in a locked office in Logan hall on UNM main campus. All paper forms will be kept for five years after the conclusion of the study, then they will be shredded using a secure (locked) service operated by the Psychology department.

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, and/or in the COINS database on a secure HIPAA compliant cloud based 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), the National Instituties of Mental Health Research Domain Criteria database (www.rdocdb.com), and OpenNeuro.org.

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.

Certificate of Confidentiality: This project will not progress without funding from the NIH, which will provide a *de facto* Certificate of Confidentiality with the award. As such, all identifiable and sensitive participant information will be protected by this mechanism.

II. *Data Analysis/Statistical Considerations*

This study is currently designed as a pilot study for the sole purpose of demonstrating feasibility in future NIH grants. There will be no formal null hypothesis significance testing.

III. *Participant Withdrawal*

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.

PRIOR APPROVALS/REVIEWED AT OTHER IRBS

N/A

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