Dear Joel Diaz-Fong,

Thank you for submitting your Stage 1 Registered Report entitled “Noninvasive Neuromodulation of Visual Perception and Neural Connectivity in Body Dysmorphic Disorder”.

I have now received reports from two expert reviewers who have provided thoughtful comments. Their feedback is generally positive, making constructive suggestions that will help strengthen the rationale for the study design, and more clearly justify certain analytical decisions.

One key issue to address is related to the power analyses presented in the Design Table in page 38. Please justify the numbers presented for expected effect sizes and auto-correlations. You will require reasonable objective reasons for why an effect would be just worth missing out on (https://doi.org/10.1525/collabra.28202) which should be done for every row in the Design Table. Exploratory tests should be excluded from the Design Table, and should not be mentioned in the Stage 1 submission, however, they can be reported in the Stage 2 in a non-pre-registered results section.

Best wishes,

Anna Furtjes

Thank you for your feedback. We have now removed all mentions of exploratory tests from the Design Table and the Stage 1 submission, following your guidance. Exploratory analyses will be appropriately reported in the Stage 2 manuscript under a non-pre-registered results section.

In addition, we have updated the power analysis in the Data Analysis section and Design Table to provide a clear justification for the expected effect sizes.

Review by Samuel Westwood, 02 Sep 2024 06:47

The authors plan to investigate body dysmorphic disorder (BDD), a psychiatric condition characterized by perceptual distortions of physical appearance, which may be linked to abnormalities in visual processing. They aim to examine the effects of combining two types of repetitive transcranial magnetic stimulation (continuous and intermittent theta burst stimulation) with a visual attention modulation paradigm on neural connectivity and visual

perceptual biases in 40 adults with BDD or subclinical BDD. I have no hesitation this would make a valid contribution to the field, provded that make the following revisions:

Major Revisions

1. The authors do not provide a clear justification for why they are using theta burst stimulation (TBS) other than citing previous studies that have demonstrated significant effects. It would strengthen the rationale if the authors could explain whether theta rhythms are specifically associated with the core symptoms of BDD or if the visual processing deficits observed in BDD are linked to disrupted theta rhythms. Establishing a causal mechanism that connects theta rhythms to the underlying pathophysiology of BDD would provide a more compelling rationale for the use of TBS in this context. Additionally, this would help clarify the neurophysiological understanding of BDD and how it relates to the observed symptoms and visual processing abnormalities.

We thank the reviewer for highlighting this point. Theta rhythms are indeed implicated in perceptual and attentional processes, particularly in tasks involving the visual processing of faces (Güntekin & Başar, 2014)**. For example, theta evoked increases in power occurs in response to inverted compared to upright faces in both occipital-temporal and parietal-occipital areas** (Borra et al., 2023)**, suggesting that theta activity may play a critical role in fine-tuning visual perceptual mechanisms. While these findings have not yet been explored in BDD, they provide a foundation for investigating the role of theta rhythms in the disorder.**

BDD is characterized by perceptual distortions and an intense preoccupation with perceived defects in appearance, particularly concerning the face and head. Given the role of theta rhythms in visual and attentional processing tasks, we hypothesize that altered theta activity may be part of the neurophysiological profile of BDD. By applying TBS, which targets theta frequency ranges, our aim is to modulate these potential neural substrates to better understand their role in the visual processing and attentional disturbances seen in BDD.

While we acknowledge that theta rhythms have not yet been directly studied in BDD, our approach provides an opportunity to explore whether theta modulation can alter perceptual biases associated with the disorder. Establishing such a causal mechanism would require further investigation, and we agree it would be speculative at this stage. However, this question represents an important direction for future research and will be discussed in detail in a Stage 2 manuscript.

Borra, D., Bossi, F., Rivolta, D., & Magosso, E. (2023). Deep learning applied to EEG source-data reveals both ventral and dorsal visual stream involvement in holistic

processing of social stimuli. *Scientific Reports*, *13*(1), 7365. https://doi.org/10.1038/s41598-023-34487-z

Güntekin, B., & Başar, E. (2014). A review of brain oscillations in perception of faces and emotional pictures. *Neuropsychologia*, *58*, 33–51. https://doi.org/10.1016/j.neuropsychologia.2014.03.014

2. The authors' description of TBS effects is potentially misleading because it does not account for the known variability in TBS responses among participants. Recent research, such as the study by Corp et al. (2020), has shown significant interindividual variability in TBS outcomes. The authors should acknowledge this variability and consider incorporating potential sources of this variation, such as baseline MEP amplitude, target muscle, age, time of day, and TBS timepoint, into their analysis model. This inclusion would enhance the accuracy and relevance of their findings.

A useful reference:
Corp, Daniel T. et al. (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration'. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 13(5), 1476-1488.

We agree with the reviewer that interindividual variability in response to TBS is a critical factor to consider. As noted, our study design focuses on comparing differential effects of iTBS vs. cTBS, and our within-person design helps to reduce interindividual variability. We recognize, however, that factors such as baseline MEP amplitude, age, time of day, and timing of stimulation could influence TBS outcomes, as highlighted in the study by Corp et al. (2020).

To address this, we have updated our methods section (page 23) to specify the inclusion of additional covariates to account for potential sources of variability. In our analysis model, we will assess and adjust for the following covariates: age, time of day, time elapsed between stimulation and scan, TBS order, resting motor threshold (MT), and depression and anxiety scores. Covariates will be retained in the final model if they reach statistical significance ($p < .05$). Non-significant covariates will be excluded to maintain model parsimony and interpretability.

3. The rationale for not including a sham condition in the study is not entirely persuasive. This issue could be addressed by either informing participants that they may receive sham or real stimulation (or even misleading them by stating that everyone will receive real stimulation), which would help manage prior expectations, or by stimulating a different, non-targeted brain region as a control to account for non-specific effects. Excluding a non-stimulation control seems like a missed opportunity, as it would provide valuable insight into whether the observed effects are due to a synergy between the stimulation and visual

processing modification or if they are primarily attributable to the visual processing intervention alone.

We appreciate the reviewer's concern regarding the lack of a sham condition. As we noted in the manuscript, our initial decision to exclude a sham group was based on the potential for placebo effects due to the notable sensations caused by TBS. Our primary aim in this study is to investigate within-subject, differential effects specifically related to the targeted brain region, focusing on the unique synergy between neurostimulation and visual processing modification.

We recognize that excluding a non-stimulation control poses some limitations in interpreting whether the observed effects are due to neurostimulation combined with visual processing modification or are primarily driven by the visual intervention alone. To address this, we plan to leverage data from a previous study, along with an ongoing study (R01MH121520) using the same task design, scanning parameters, and inclusion/exclusion criteria, to provide a comparative analysis. This approach should help clarify the unique contributions of stimulation without the need for a sham condition within this study itself.

Regarding the reviewer's suggestion of stimulating an alternate, non-targeted brain region, we agree that this could potentially serve as a valuable control. However, given the limited research on the effects of stimulating other brain regions in BDD, there is a possibility that any alternative site chosen could yield indirect effects on the same cognitive or emotional processes we aim to study. Future studies could certainly expand upon our findings by including a sham or an alternate control region to further isolate specific mechanisms.

We thank the reviewer for these insightful suggestions and agree that such controls would enhance the rigor of future studies, as they are well-suited for further exploration once we have established a foundational understanding of the targeted neurostimulation effects in BDD.

4. The authors briefly mention the possible synergistic effect of TBS and visual attention modulation but do not adequately account for the fact that the effects of TBS, like any form of non-invasive brain stimulation (NIBS), are state-dependent. The final outcome is likely the net result of the ongoing brain activity and its interaction with TBS effects. This point reinforces the concerns raised in revisions 2 and 3. While it is unclear how the authors might address this issue, it is an important consideration that should be discussed and potentially factored into their analysis and interpretation.

We thank the reviewer for underscoring the importance of considering the state-dependent nature of TBS effects. We agree that the final impact of TBS likely reflects the interaction between ongoing brain activity and the stimulation effects, which is particularly relevant given the state-dependent nature of non-invasive brain stimulation.

To address this, we are collecting several state-dependent measures that are highly relevant to BDD symptomology, such as the Body Image States Scale, the State-Trait Anxiety Inventory, and the Profile of Mood States. These measures will allow us to evaluate participants' current affective states, which can inform our understanding of the interactions between these states and TBS effects.

Additionally, while our main brain connectivity analysis focuses on an induced state that occurs after TBS, we will incorporate these state-dependent measures into our analysis model as exploratory covariates or moderators. This approach will enable us to explore whether the effectiveness of TBS is influenced by participants' pre-stimulation states, adding depth to our interpretation of TBS effects in relation to BDD-specific symptoms. Since this is an exploratory analysis, it will be appropriately reported in a Stage 2 manuscript under a non-pre-registered results section.

Minor Revisions

1. Consider reducing the use of acronyms throughout the manuscript. For example, the sentence "that iTBS will increase DEC within the DVS and reduce DEC within the VVS during naturalistic own-face viewing, while cTBS will result in opposite effects: decreased DEC within the DVS and increased DEC within the VVS" was particularly difficult to parse. While the use of "TBS" is understandable, it would improve readability to spell out other terms, especially given that there does not appear to be a strict word count limitation.

We agree with the reviewer that the sentence could be clearer. We have revised the text to reduce acronym use and improve readability. For example, the sentence now reads: "We hypothesize that iTBS will increase dynamic effective connectivity within the dorsal visual stream and decrease dynamic effective connectivity within the ventral visual stream during naturalistic own-face viewing."

Review by anonymous reviewer 1, 13 Sep 2024 10:59

This proposed study is an interesting and innovative approach to BDD, combining both aspects of mechanistic understanding, and neurobiologically-grounded intervention. There

is a good balance of objective and questionnaire-based assessments. It has strong potential to contribute to the field in this area. Here are a series of additional comments:
- Is there any evidence that cTBS could make the participants' symptoms worse? It would be reassuring to the reader to know whether or not this could be the case. It is appreciated this study already has ethical approval, but if there is a possibility of symptom exacerbation, then knowing this would be an important part of the informed consent process.

Thank you for your insightful question. To address your concern, it is important to emphasize that the risk of symptom exacerbation following cTBS is minimal based on decades of research on TMS. Specifically, the procedures used in this study have been classified as minimal risk by numerous ethical and regulatory bodies, meaning they do not pose harm or discomfort beyond what is typically encountered during routine physical or psychological evaluations.

The known risks associated with TMS include occasional mood changes or anxiety. We mitigate these risks by ensuring participants are fully informed about the procedures during the consent process. While mild mood changes or anxiety have been observed on rare occasions, there is no evidence to suggest that cTBS worsens pre-existing symptoms in participants with psychiatric conditions. In fact, several studies have demonstrated the therapeutic potential of cTBS protocols in treating various symptoms, including mood and anxiety disorders, without worsening symptoms.

- Please could more justification be explicitly referred to in the selection of the TMS target coordinates? Lines 302-303.

We have revised the manuscript to describe the selection of the target region. The following sentence has been modified (lines 302-307):

"The BrainSight2 neuronavigation system will facilitate MRI-guided coil placement at the target foci, which were determined from meta-analysis of functional brain imaging studies for "dorsal visual stream" (Neurosynth; https://neurosynth.org/), yielding the following foci (MNI co-ordinates): left lateral parietal cortex (-38, -38, 46) and right lateral parietal cortex (32, 44, 46), corresponding to CP3 and CP4 respectively on the EEG 10-10 system."

- Please can it be made clearer earlier in the paper and in figure 1 that this is a crossover design, where all participants will receive both iTBS and cTBS.

Thank you for your helpful comment. We have revised the manuscript to make it clearer earlier in the text that this is a crossover design in which all participants will receive both iTBS and cTBS. Specifically, we have clarified this point in the

introduction and methods sections to ensure transparency. Additionally, we have updated Figure 1 to explicitly indicate the crossover nature of the study. We hope these changes adequately address your concerns and provide greater clarity for the reader.

- Participants' compliance with the fMRI task is being monitored via eye-tracking. When fMRI data is being preprocessed, how will this be incorporated into quality assurance procedures?

Thank you for your comment. To clarify, eye-tracking will be used during the scanning session to monitor participants' compliance with the task in real-time. However, these measures will not be incorporated into the data preprocessing pipeline. Our quality assurance procedure will focus on evaluating participants' engagement during the scan itself. If a participant is found to be non-compliant during the task (e.g., consistently failing to maintain fixation or not following task instructions), the corresponding session will be excluded from further analysis. We have included this detail in lines 334-336.

- Please could it be made explicit which ROIs are considered higher and lower within their respective visual streams?

Thank you for your helpful feedback. We have revised the manuscript to explicitly clarify which ROIs are considered higher and lower within the visual streams. The following sentence has been added (lines 372-377):

"Twelve intra-hemispheric connections will be chosen and divided into 4 categories: 1) lower dorsal visual stream [calcarine to superior occipital gyrus (SOG)], 2) higher dorsal visual stream [SOG to inferior parietal lobule (IPL); SOG to superior parietal lobule (SPL)], 3) lower ventral visual stream [calcarine to inferior occipital gyrus (IOG)], and 4) higher ventral visual stream [IOG to fusiform gyrus (FG); IOG to inferior temporal gyrus (ITG)]."

-Concerning the statistical analyses, it is very important that the investigators be able to differentiate effects that are driven by iTBS vs cTBS. We don't want to be in the position where we're unable to say whether an apparently significant difference is due to (a) iTBS-mediated potentiation, with cTBS having minimal effect, or (b) iTBS having minimal effect, and cTBS-mediated inhibition. For the GLMs described from line 395, I'm not entirely sure from this model description if this would be the case. It would settle the matter if we could see the proposed model formulae.

Thank you for this insightful comment. We agree that differentiating the effects of iTBS versus cTBS is essential to accurately interpret our findings. To address this,

we will be explicitly modeling the effects of each TBS condition (iTBS and cTBS) along with *Task condition* and *Visual stream level* to isolate their contributions to connectivity. The proposed model is as follows:

$$\text{Connectivity} = \beta_0 + \beta_1(\text{Task condition}) + \beta_2(\text{Visual stream level}) + \beta_3(\text{Task condition} \times \text{Visual stream level}) + \beta_4(\text{DVARS}) + (1|\text{Participant}) + \varepsilon$$

This model includes the following:

- **Although not explicitly shown in the above formula, TBS type *(iTBS vs. cTBS)* is analyzed in separate models to assess their individual contributions to connectivity. This ensures we can determine whether effects are driven by iTBS-mediated potentiation or cTBS-mediated inhibition.**
- **The interaction terms *(Task condition × Visual stream level)* enable us to examine how changes in connectivity during naturalistic own face viewing (before and after visual attention modulation) interact with processing in different visual streams.**
- **The random effect *(1|Participant)* accounts for within-subject variability, ensuring that individual differences are appropriately modeled in the mixed-effects framework. This allows us to accurately interpret connectivity changes across Task condition and Visual stream level without confounding effects from between-subject variability.**

We believe this structure will enable a clear differentiation of iTBS and cTBS effects on connectivity, addressing the reviewer's concerns. Thank you for the opportunity to clarify our approach.

- Seeing the formulae would also help provide reassurance that the repeated-measures aspect of this design is being appropriately accounted for/represented ie a mixed effects model.

We appreciate the reviewer's request for clarification. We have added the model formulae in the methods section on page 23.

- The investigators allude to a desire to incorporate depression/anxiety measures in their analysis - please could they describe how?

We have revised the methods section (lines 405-409) to reflect these additions:

"For each GLMM, we will assess potential sources of interindividual variability, including age, gender, time of day, time elapsed between stimulation and scan, TBS order, resting MT, and depression and anxiety measures. Covariates will be retained in

the final model only if they reach statistical significance ($p < .05$). Non-significant covariates will be excluded to maintain model parsimony and interpretability."