Responsive nucleus accumbens deep brain stimulation restores eating control in severe obesity

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Abstract

Cravings that precede loss of control (LOC) over food consumption present an opportunity for intervention in patients suffering from binge eating disorder (BED). Here, we used responsive deep brain stimulation (DBS) to record NAc electrophysiology during food cravings preceding LOC eating in two patients with BED and severe obesity (NCT03868670). Increased NAc low-frequency oscillations prominent during food cravings were used to guide DBS delivery. Over 6 months, we observed improved self-control of food intake and weight loss. These findings provide early support for restoring inhibitory control with electrophysiologically-guided NAc DBS. Further work is required to determine scalability of this approach. Trial Registration # NCT03868670.

Introduction

Loss of control (LOC) eating, or the subjective sense that one cannot stop eating, is associated with binge eating – defined by the consumption of an objectively large amount of food in a short period of time accompanied by a sense of LOC.[1] LOC eating is often characterized by the loss of inhibitory control in response to appetitive cues and cravings leading to binge eating[2]. Recurrent and distressing episodes of binge eating are the key features of binge eating disorder (BED). BED is the most common eating disorder, affecting up to 3 percent of U.S. adults, and is the most severe form of LOC eating based on volume of food consumed[1]. It is associated with obesity, decreased quality of life and premature mortality.[3]

Most treatments for obesity fail to address LOC eating directly, limiting the efficacy of even the most aggressive interventions such as bariatric surgery.[4,5] Clinical evidence supports a role of cravings for preferred food, or intense desires to consume specific palatable foods, prior to the onset of LOC and binge eating.[6,7] Particularly in individuals who are overweight or obese, food cravings have been linked with LOC among those diagnosed with BED.[8] Given this, recent studies have examined neural signals associated with food craving in the pursuit of identifying a biomarker used to trigger deep brain stimulation (i.e., responsive DBS or rDBS) and inhibit onset of LOC eating when patients may be most at-risk.

In the effort to identify such a craving biomarker, previous work in mice found that anticipation of a high-fat food reward was associated with increased low-frequency oscillatory power in the NAc.[9] This work supported a growing body of evidence across species reporting electrophysiological, neurochemical, and functional neuroimaging activities within circuits involving the NAc that correlate to reward anticipation,[10–13] and that predict consequential behavioral outcomes.[14] Using low-frequency delta-band power as a biomarker to trigger delivery of a brief train of high-frequency electrical stimulation to the NAc (here after referred to as rDBS) resulted in significant and lasting attenuation of binge-like eating in mice sensitized to high fat food,[9] while conventional, continuous DBS appeared to lose efficacy over time.[15,16]

Here, we report the proof of concept in this first-in-human study designed to characterize human NAc electrophysiology of craving as it relates to LOC eating. We sought to identify changes in NAc electrophysiology associated with moments of food craving and LOC eating during controlled in-clinic behavioral tasks and to assess the generalization of this effect to LOC eating events in a naturalistic setting and outside the behavioral laboratory. Finally, we implemented rDBS triggered by NAc electrophysiology identified in behavioral and naturalistic assessments, and report here initial results on the potential efficacy of this novel intervention. This study was performed under a U.S. Food and Drug Administration Investigational Device Exemption (G180079) using the NeuroPace Responsive Neurostimulation (RNS) System[17].

Methods

PRESTUDY PROCEDURES

Two adult women with BED and treatment-refractory severe (grade III) obesity, despite bariatric surgery were recruited for this study, approved by Stanford's Institutional Review Board (IRB-46563) (see appendix for participant characteristics). Designed with a staggered enrollment, each subject progressed through the study stages shown in **Fig. 1A**. Both subjects underwent stereotactic implantation of bilateral depth electrodes, each with four contacts.[18] The two distal contacts were positioned in the NAc and the two proximal contacts traversed the anterior limb of the internal capsule (Fig. 1**B**).[19]

RECORDING PHASE

Immediately following implantation, subjects entered a 6-month recording phase, during which naturalistic in-lab assessments and ambulatory real-world assessments were performed to identify an electrophysiological biomarker for rDBS in the consecutive stimulation phase. From each hemisphere, activity was recorded from the ventral and dorsal NAc (see appendix for details). Subjects underwent two assessments to evaluate NAc electrophysiology during: 1) anticipation (pre-consumption) of food during standard meals and LOC eating (i.e., Multi-Item Buffet assessment; in-lab naturalistic testing); and 2) states of hunger and craving (pre-consumption) (i.e., ambulatory assessment; real-world testing).

STIMULATION PHASE

Following the recording phase, both subjects underwent single-blinded stimulation survey testing in which they received brief bursts of electrical stimulation across all electrode contacts to screen for acute effects. This was followed by a single-blinded, staged, on-off stimulation safety testing period to assess for possible side effects of rDBS. Subjects then entered the 10–12 month open-label stimulation phase of the study. In this phase, rDBS was delivered using a bipolar montage of the two NAc electrode contacts. Both subjects received bilateral NAc rDBS via depth electrodes connected to a NeuroPace RNS system to detect and inhibit LOC eating events. Stimulation was delivered at 125 Hz in two 5 second bursts with a charge density of 0.5–1.5 μC/cm.[17] Detections and stimulations occurred approximately 400 times/day with a stimulation limit set to 700 bouts (or approximately 117 min) per day in order to limit unnecessary

stimulation at night. Based on the recording phase, each subject's device was programmed to detect brief increases in low-frequency activity in both the left and right ventral NAc (see appendix). These detections of low-frequency activity triggered bilateral NAc rDBS (~ 1μC/cm^2 charge density, 10s duration). Low-frequency triggered bilateral stimulation has been well tolerated by both subjects. Neither subject 1 nor 2 experienced a serious adverse event, and all reported events were self-limited (**Table S4**). Examination of sensitivity and specificity can be found in the appendix (**Figures S1, S2**).

Results

RECORDING PHASE

MULTI-ITEM BUFFET: NAC ELECTROPHYSIOLOGY DURING IN-LAB LOC EATING. In this assessment, we investigated each subject's LOC by modeling the at-risk environment in a controlled setting[20]. Using mood provocation (see appendix), we assessed LOC (1–5 Likert severity scale) during presentation of a high calorie buffet of the subject's preferred foods while recording synchronized video-NAc LFP (Local Field Potential) activity. Analogous to our pre-clinical work, we analyzed and compared bite onset during the buffet to standard meals. Results showed low-frequency power increases immediately prior to LOC eating. Specifically, increases in left ventral NAc low-frequency (2–8 Hz) power were observed for both subjects during LOC immediately preceding (within 2 seconds) the videoed bite onset (see appendix) (mean ± s.e. dB power [V^2/Hz]: Subject 1, 2.4 ± 1.5, n = 16 bites; Subject 2, 5.6 ± 3.1, n = 12 bites). In contrast, increases in low-frequency power were not observed immediately prior to bites during standard meals (Subject 1, 0.6 ± 1.0, n = 15 bites; Subject 2, 0.3 ± 0.9, n = 11 bites) (Fig. 1**C**, Student's t-test, $p < 0.05$). There were no statistical changes in any of the other recorded frequency bands in either subject (Student's t-test, $p > 0.05$).

AMBULATORY ASSESSMENT: NAC ELECTROPHYSIOLOGY DURING REAL-WORLD LOC EATING EVENTS. We analyzed electrophysiology acquired during real-world behavioral states (see appendix) to validate the lab findings. Low-frequency power increases during LOC eating were corroborated with real-world assessments. Specifically, significantly higher low-frequency oscillatory power (Fig. 2**A**) in bilateral ventral NAc was found during subject-reported LOC eating events (craving-red trace, mean ± s.e. power [V^2/Hz]: Subject 1, left NAc: 0.21 ± 0.11, right NAc: 0.16 ± 0.06, n = 10 events; Subject 2, left NAc: 0.58 ± 0.14, right NAc: 0.21 ± 0.07, n = 71 events) when compared to control periods (control-black trace, Subject 1, left NAc: 0.1 ± 0.04, right NAc: 0.04 ± 0.01, n = 9 events; Subject 2, left NAc: 0.19 ± 0.04, right NAc: 0.09 ± 0.04, n = 80 events) and periods of hunger (hunger-blue trace, Subject 1, left NAc: 0.06 ± 0.01, right NAc: 0.03 ± 0.01, n = 13 events; Subject 2, left NAc: 0.27 ± 0.11, right NAc: 0.11 ± 0.03, n = 37 events) (Fig. 2**A**, one-way ANOVA, Subject 1, left NAc: $f = 3.50$, $P = 0.04$, right NAc: $f = 4.95$, $P = 0.03$; Subject 2, left NAc: $f = 5.14$, $P = 0.02$, right NAc: $f = 0.07$, $P = 0.93$). Consistent with the in-clinic tasks, there were no differences in any other frequency band during at-risk moments in the ambulatory setting.

SIGNAL DETECTION: BILATERAL NAC DETECTION. For each subject, we programmed the device to detect brief increases in low-frequency activity in both the left and right ventral NAc. To confirm that the signal

being detected was in the low-frequency range, we analyzed the power spectra of the NAc LFP activity in the 5 seconds prior to a detection and found that the Area detectors (see appendix) were detecting low-frequency activity in the left and right ventral NAc (Fig. 2**B**). For this analysis, we compared detection made in stored LFPs during reported LOC eating events and awake events. For Subject 1, increased low-frequency power compared to baseline NAc LFP signal (average 2-minute window) was identified in 74.4% (67/90) of reported LOC eating event detections and 63.2% (84/133) of the awake detections ($X2(1,N = 223) = 24.54, p < 0.05$). For Subject 2, increased low-frequency power was identified in 76.9% (30/39) reported LOC eating event detections and 45.8% (22/48) awake detections ($X2(1,N = 87) = 14.82, p < 0.05$).

STIMULATION PHASE

CHANGE in LOC EATING and Weight. Both subjects reported an increased sense of self-regulation and control over food intake specific to cravings and related eating behavior. Further, both subjects showed a decrease in the reported frequency of LOC eating events from baseline to 6-months post-stimulation (i.e. the primary endpoint), as assessed by the Eating Disorder Examination (EDE), and LOC severity, as assessed by the Eating Loss of Control Scale, across the 28-day period during the baseline month compared to 6-months post-stimulation month (LOC Frequency: Subject 1 = 80% decrease; Subject 2 = 87% decrease; LOC episode severity: Subject 1: 9-point improvement ($p = 0.09$); Subject 2: 15-point improvement ($p = 0.05$)) (Fig. 3**A,B**). Notably, by the end of the 6-month follow-up period, Subject 1 exhibited substantial improvement in BED severity, while Subject 2 no longer met criteria for BED (i.e., fewer than average of 4 binge eating events per-month over the prior consecutive 3 months for no more BE diagnosis), which met our primary endpoint (Fig. 3**C**). Corroborating their subjective reports (Fig. 3), 6-month outcomes showed a decrease in body weight (kg and % reduction) and BMI for both subjects: Subject 1 = -5.9 kg, -4.5%, and − 2.2 kg/m^2, respectively; Subject 2 = -8.2 kg, -5.8%, and − 2.9 kg/m^2, respectively)(Fig. 3**D,E**).

Discussion

In summary, this study identified NAc low-frequency oscillatory power as a signal associated with LOC craving, and then implemented this biomarker to guide rDBS delivery in two subjects with BED and severe obesity. In the recording phase, in-lab assessments implicated NAc low-frequency signalling during naturalistic LOC eating. The generalizability of this signal to real-world settings was then corroborated by our finding that low-frequency oscillatory power was increased during real-world LOC eating events compared to non-LOC events. In the stimulation phase, 6 months of bilateral NAc rDBS triggered by low-frequency power was found to improve LOC eating, as well as reduce body weight and BMI. Optimization of stimulation parameters is still ongoing in both subjects, and four additional subjects are expected to be implanted following a supplement approval to our investigational device exemption. We encountered early challenges when capturing LOC eating events in the real world. A training period was necessary prior to surgery for both subjects to learn to identify and document their LOC eating behaviors. This involved having a psychiatrist (DS) with expertise in obesity and eating disorders discuss with each patient her

personal understanding of LOC eating. As we report (see appendix), while sensitivity of low-frequency detections to LOC eating was high, low-frequency oscillations in the NAc were not always specific to food craving and LOC eating compared to non-LOC eating events. Ongoing work seeks to optimize detection algorithms and improve the sensitivity and specificity of rDBS for LOC eating. Further, real-world LOC electrophysiology detected from ambulatory recordings was specific to bilateral, ventral NAc delta (2-4Hz), whereas in-lab experiments found effects in both delta and theta (2-8Hz) and were limited to the left ventral NAc. In addition, because real-world data capture was not time-locked to specific bite events during LOC and standard meals, the ambulatory and multi-item buffet data reflect different time windows respective to the LOC events. We also note that while the frequencies within which we found our effects here contained the delta signal identified in mice[9], the effects from in-lab testing were broader and inclusive of theta frequencies. Importantly, one difficulty with the low-frequency biomarker signal is its presence during normal physiological processes such as sleep[21,22]. To account for detection and stimulation during sleep, we limited rDBS delivery to awake hours (7am-10pm). Finally, the upfront cost of implantable devices is high; thus long-term follow-up of LOC eating as well as BMI beyond the study period will be necessary to assess societal cost-effectiveness of this intervention based on our decision analyses[23].

In conclusion, NAc rDBS improved LOC eating frequency and severity in two patients with BED and severe obesity. These findings were associated with weight loss even during this early follow-up period, suggesting patients can lose weight without instruction to change their diet or physical activity (efforts which are often unsuccessful). This is a testament to the potential clinical significance of this novel intervention and supports continued study in this FDA-guided first-in-human, early feasibility trial.

Declarations

Acknowledgments

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Competing Interests

No funding from NeuroPace was received for this study nor were data analyses reported here conducted by NeuroPace employees. CHH, RSS, and CER have patents related to sensing and brain stimulation for the treatment of neuropsychiatric disorders.

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Figures

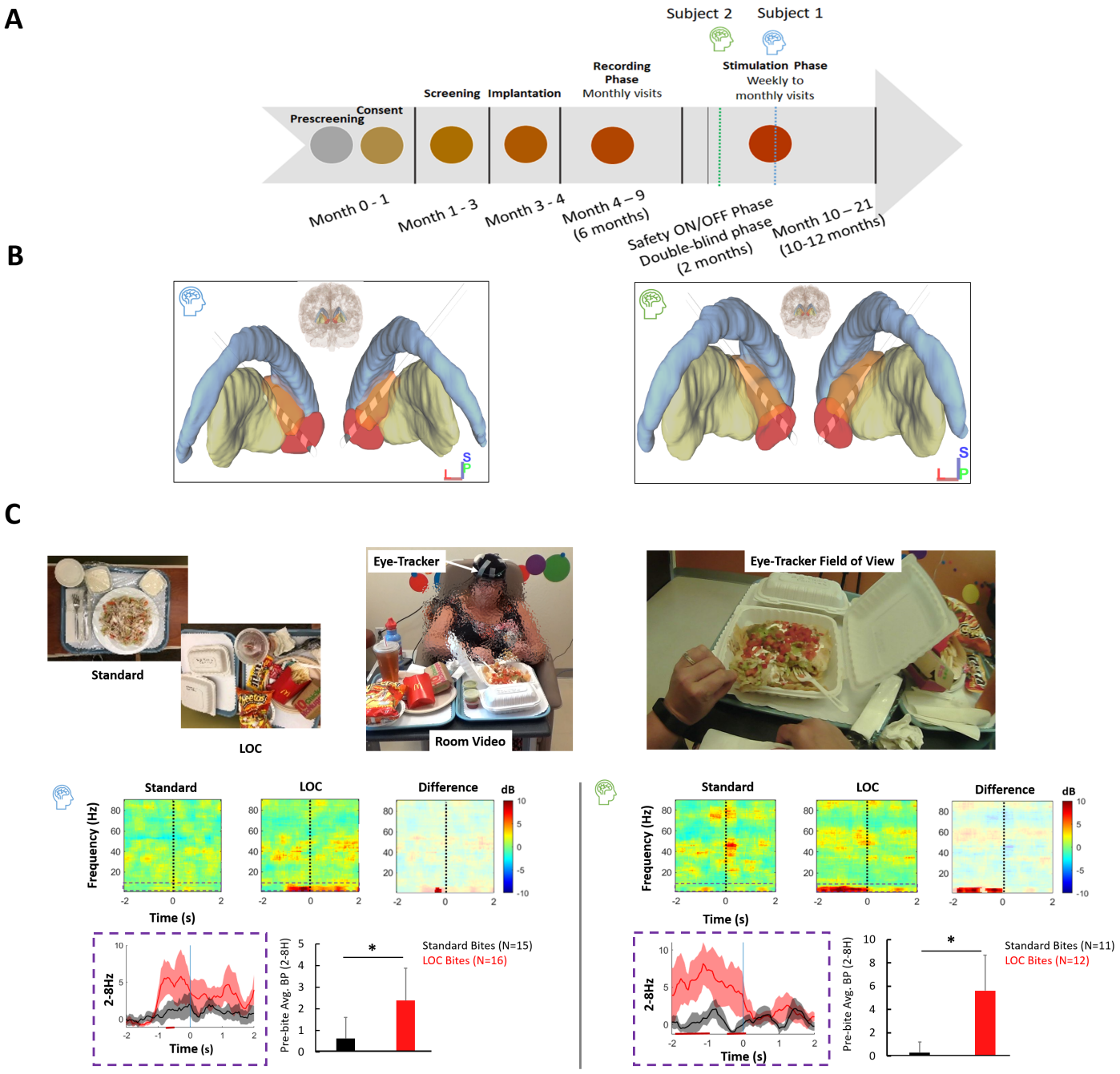

Figure 1

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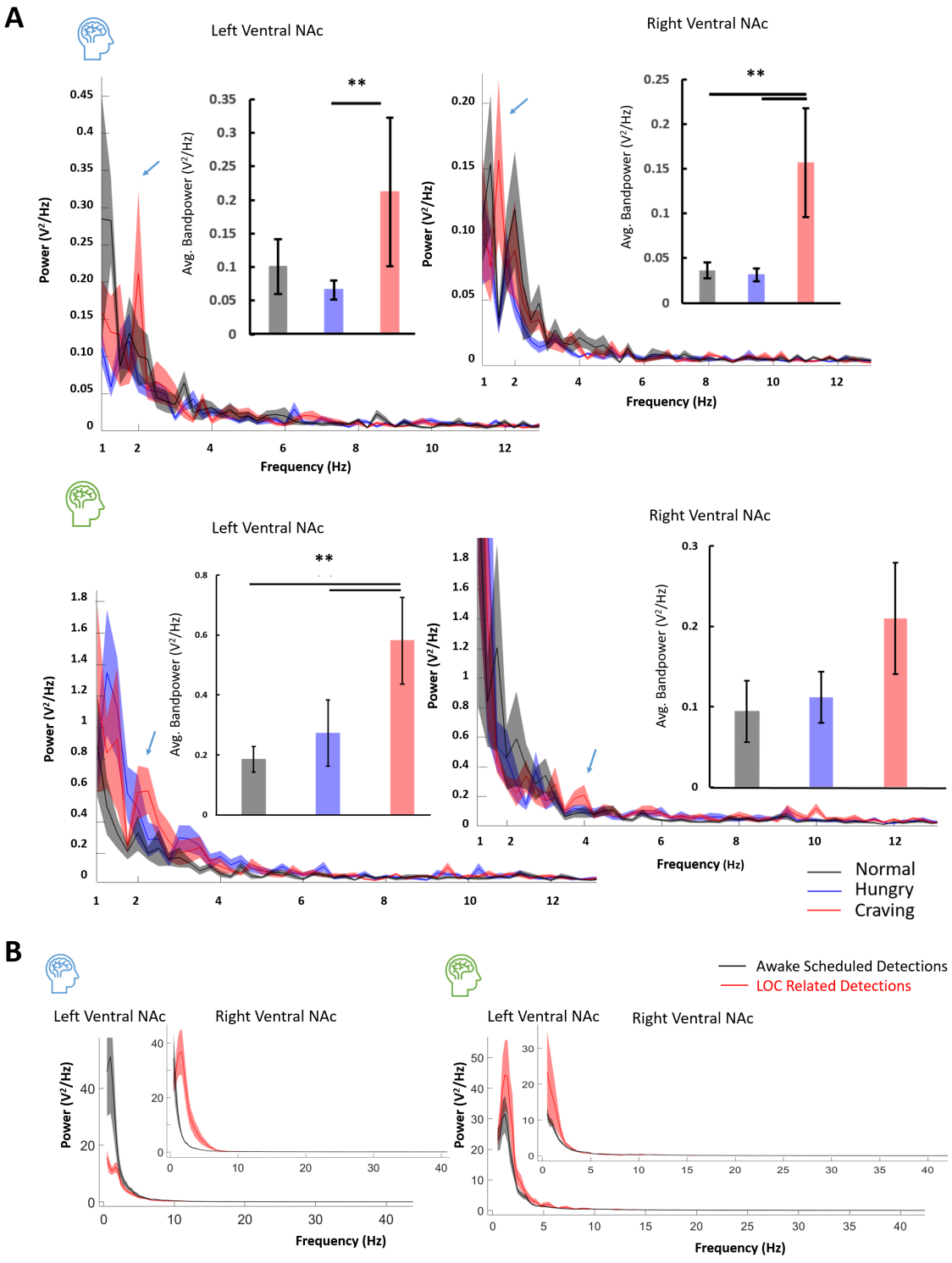

Figure 2

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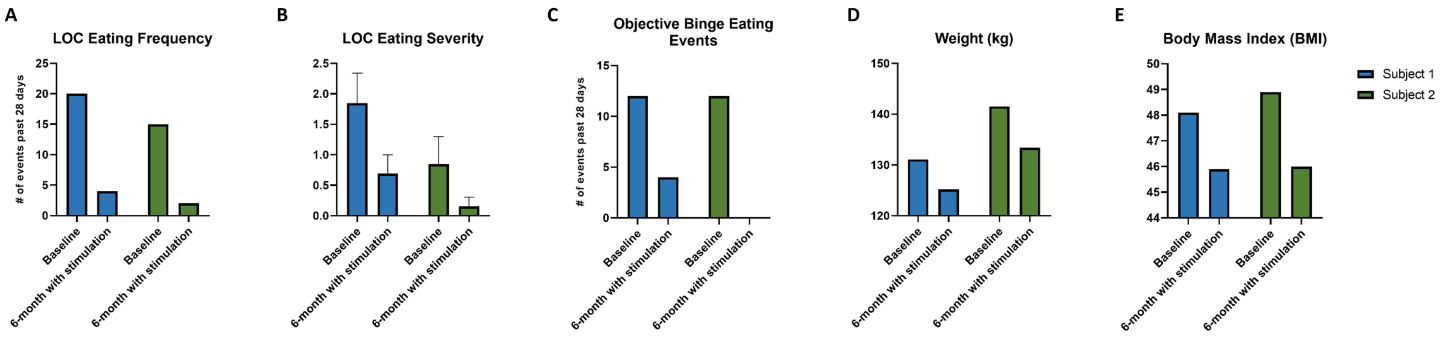

Figure 3

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Supplementary Files

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