

Brain activity associated with breakthrough food preoccupation in an individual on tirzepatide

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Obesity and related conditions are associated with distressing food preoccupation that often culminates in dysregulated eating behaviors. Incretin-based therapies can reduce excessive weight in obesity, but their impact on dysregulated eating behaviors remains largely unexamined. Understanding how these pharmacologics engage the brain's mesolimbic circuitry may inform the expansion of their therapeutic potential. We report a rare, first-in-human exploration of the physiological action of these therapies by examining the electrophysiology directly within the human nucleus accumbens. After a short-term course of tirzepatide, the patient-participant exhibited increased severe food preoccupation episodes, which were preceded by an increased delta–theta frequency (≤ 7 Hz) power in the nucleus accumbens region. We propose that the effects of an incretin-based therapy (tirzepatide) on food preoccupation may be associated with modulation of aberrant activity within this key hub of human mesolimbic circuitry.

Eating behaviors are regulated by homeostatic (for example, eating based on energy needs) and hedonic (for example, eating based on pleasure) processes, involving the hypothalamic and brain stem circuits as a hub for the former, and a mesolimbic circuit (including the nucleus accumbens (NAc)) for the latter^{1–3}. These systems are highly interactive and are further influenced by other intermediate brain regions to include the complex motivational processes of ingestion^{1,4,5}. As such, the distinction between homeostatic and hedonic eating as entirely separate entities is increasingly viewed as a conceptual oversimplification^{1,4}. There is a preponderance of receptors of incretin-based therapies (for example, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)-based receptor agonists) in central

nervous system nuclei, including the hypothalamus and NAc, which regulate energy balance and reward processing^{6,7}, underlying their therapeutic potential for obesity and type 2 diabetes^{8–10}.

However, the physiological action of incretin-based therapies specifically on the mesolimbic circuitry to alter human eating behaviors remains unexplored. In concordance with homeostatic processes, the mesolimbic system contributes to food-related motivation and its dysregulation underlies disturbances in food preoccupation (that is, heightened or persistent reactivity to food cues¹¹). Food preoccupation is often associated with dysregulated eating behaviors, ranging from loss-of-control eating (that is, eating with a subjective feeling of loss of control and associated distress) to binge eating (that is,

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the most extreme bout of loss-of-control eating). These debilitating symptoms affect up to 60% of patients with obesity and related eating disorders^{11–13}. Although aberrations in the mesocorticolimbic system, hypothalamus and brain stem are implicated in both obesity and binge eating disorder^{3,4,14}, patients with binge eating disorder may be more prone to these symptoms than those with obesity in the absence of binge eating disorder because of the degree of reward hypersensitivity and food impulsivity involving mesocorticolimbic dysregulation^{14–17}. While incretin-based therapies have exhibited some promise in ameliorating food preoccupation and dysregulated eating behaviors^{9–11}, early data suggest a tolerance effect for food preoccupation^{18,19}. Direct measures of neural activity could yield insights into how incretin-based therapies engage the mesolimbic circuitry and help broaden their therapeutic scope to related eating disorders, possibly by identifying a target engagement biomarker (that is, a neural signal that reflects functional modulation of a brain region in response to treatment).

Intracranial electroencephalography (iEEG), acquired using implanted depth electrodes, provides a rare opportunity to directly measure neural activity within human brain circuitry. iEEG has recently been used to identify electrographic biomarkers of neuropsychiatric disorders^{20–22}. An ongoing early feasibility trial (ClinicalTrials.gov registration [NCT03868670](https://clinicaltrials.gov/ct2/show/study/NCT03868670)) has recruited participants with treatment-refractory obesity and loss-of-control eating to identify related iEEG activity²³. Participants' dysregulated eating episodes were classified as loss-of-control eating rather than binge eating because they did not consistently meet the criteria for eating an objectively large amount, probably because of their restricted gastric volume after bariatric surgery. We previously reported iEEG activity within a low-frequency band (2–8 Hz), which ramped up during periods of loss-of-control eating from previous participants²¹. In the present study, we used a first-of-its-kind opportunity to report a case study provided by participant 3 (Fig. 1a–d) to investigate an electrographic biomarker associated with the frequency of severe food preoccupation while taking tirzepatide, using preliminary findings from participants 1 and 2 as a reference. The preliminary findings presented in this article for participants 1 and 2 differ from a previous report²¹ that aimed to guide responsive deep brain stimulation (rDBS) with specificity for hedonic states. Instead, in the present study, we focused on food preoccupation, reflecting a conceptual shift that dysregulated eating behaviors are a result of disruption in both hedonic and homeostatic processes (for more information, see Methods)^{1,4,11}.

We analyzed ambulatory iEEG recordings from the NAc in participants 1 and 2 during the biomarker discovery phase. During this phase for both participants, the delta–theta band (≤ 7 Hz) power in the ventral NAc during the severe food preoccupation states was significantly higher than that of control states in both the left hemisphere (permutation testing, $P = 2.1035 \times 10^{-6}$ (participant 1) and 2.48443×10^{-11} (participant 2)) and right hemisphere ($P = 4.7013 \times 10^{-5}$ (participant 1) and 4.2414×10^{-8} (participant 2)) (Fig. 1e–h left, Supplementary Fig. 3 and Supplementary Tables 1 and 2). Moreover, both participants reported a high number of severe food preoccupation episodes (that is, moments of feeling intense food noise; Supplementary Fig. 4). After the biomarker discovery phase, and thus after a few months of responsive stimulation triggered by this biomarker detection, the delta–theta band power in the ventral NAc during severe food preoccupation states was indistinguishable from that of control states in both hemispheres of both participants (left hemisphere: $P = 0.0519$ (participant 1) and 0.6433 (participant 2); right hemisphere: $P = 0.5129$ (participant 1) and 0.4227 (participant 2); Fig. 1e–h right, Supplementary Fig. 3 and Supplementary Tables 1 and 2). The number of severe food preoccupation episodes during the stimulation phase also decreased (Supplementary Fig. 4). Thus, including the previous findings^{21,24}, we postulated that the delta–theta band power (≤ 7 Hz) could serve as a biomarker reflecting a state of heightened propensity for severe food preoccupation, as observed in the changes of the number of episodes.

We hypothesized that the effects of tirzepatide on food preoccupation are related to modulation of this delta–theta band biomarker in the NAc, a key hub of the mesolimbic reward circuitry where incretin receptors are also expressed^{6,7}.

Unlike participants 1 and 2, participant 3 exhibited a lengthy absence of severe food preoccupation in months 2–4 after surgery (Fig. 2a and Supplementary Fig. 7), coinciding with a tirzepatide dose increase that occurred before surgical implantation. During this period, the delta–theta band (≤ 7 Hz) power during the severe food preoccupation states was indistinguishable from that of control states (Fig. 2b, under the green bar, and Fig. 2c,d) in both the left (permutation testing, $P = 0.8105$) and right ($P = 0.1011$) hemispheres. There were also no differences in other higher frequencies. These findings are markedly different from those from participants 1 and 2 (Fig. 1e–h, left) and our prior reports^{21,24}. The length of this quiescent period (months 2–4) was later corroborated by using an algorithm that identified the transition point corresponding to the most pronounced change in power values within the delta–theta frequency band (≤ 7 Hz; Supplementary Fig. 8; see Methods for more detail)^{25,26}.

In contrast, during months 5–7, the delta–theta band biomarker emerged and the participant began to report breakthroughs in severe food preoccupation despite the maximum dose of tirzepatide (Fig. 2a,b, under the pink bar; increased power values in the delta–theta band (≤ 7 Hz) are noted in yellow). During this period, a prominent delta–theta oscillatory waveform was observed (Supplementary Fig. 9). Moreover, the delta–theta band (≤ 7 Hz) power from severe food preoccupation states was significantly higher than that of control states in the left hemisphere (permutation testing, $P = 1.5310 \times 10^{-22}$) and right hemisphere ($P = 1.0887 \times 10^{-6}$) (Fig. 2e,f). After the change in biomarker, the number of severe food preoccupation episodes increased to seven per month (Fig. 2a).

We present a unique case that provided a serendipitous opportunity to investigate the associated electrophysiology of an incretin-based pharmacologic in the human NAc. A profoundly low number of severe food preoccupation episodes (and a reduction in body weight) during months 2–4 (excluding month 1 after surgery because of a potential implantation effect²⁷) was consistent with a concomitant increase in tirzepatide for diabetes management^{11,28}. Importantly, this lengthy absence of severe food preoccupation after surgery contrasted with participants 1 and 2 (Supplementary Fig. 7). During this period, participant 3 also exhibited an absence of the expected delta–theta band (≤ 7 Hz) biomarker in the ventral NAc. The delta–theta band biomarker emerged during months 5–7 in participant 3, which preceded a breakthrough in severe food preoccupation despite tirzepatide^{18,19}. Therefore, the delta–theta band power during severe food preoccupation states may reflect a state of heightened propensity for severe food preoccupation, as observed in the changes of the number of episodes. The biomarker is present (or increased compared to control) when severe food preoccupation occurs more frequently and is absent (or indistinguishable from control) when severe food preoccupation occurs less frequently.

These preliminary results suggest that tirzepatide administration may be associated with the modulation of the delta–theta band (≤ 7 Hz) biomarker in the human NAc. All three participants exhibited a substantial increase in delta–theta power during severe food preoccupation states in both hemispheres (that is, six hemispheres) during the biomarker discovery phase. For participant 3, there was a temporal lag between the emergence of the biomarker in month 5 and the most severe breakthrough of food preoccupation in month 7, which could be specific to tirzepatide. In particular, a supplementary cross-correlation analysis suggested a 7-week lag (Supplementary Fig. 10). Additionally, the effect size of the power difference between severe food preoccupation and control states was more pronounced, and the transition point was only identified in the left NAc of participant 3, suggesting a potential laterality bias.

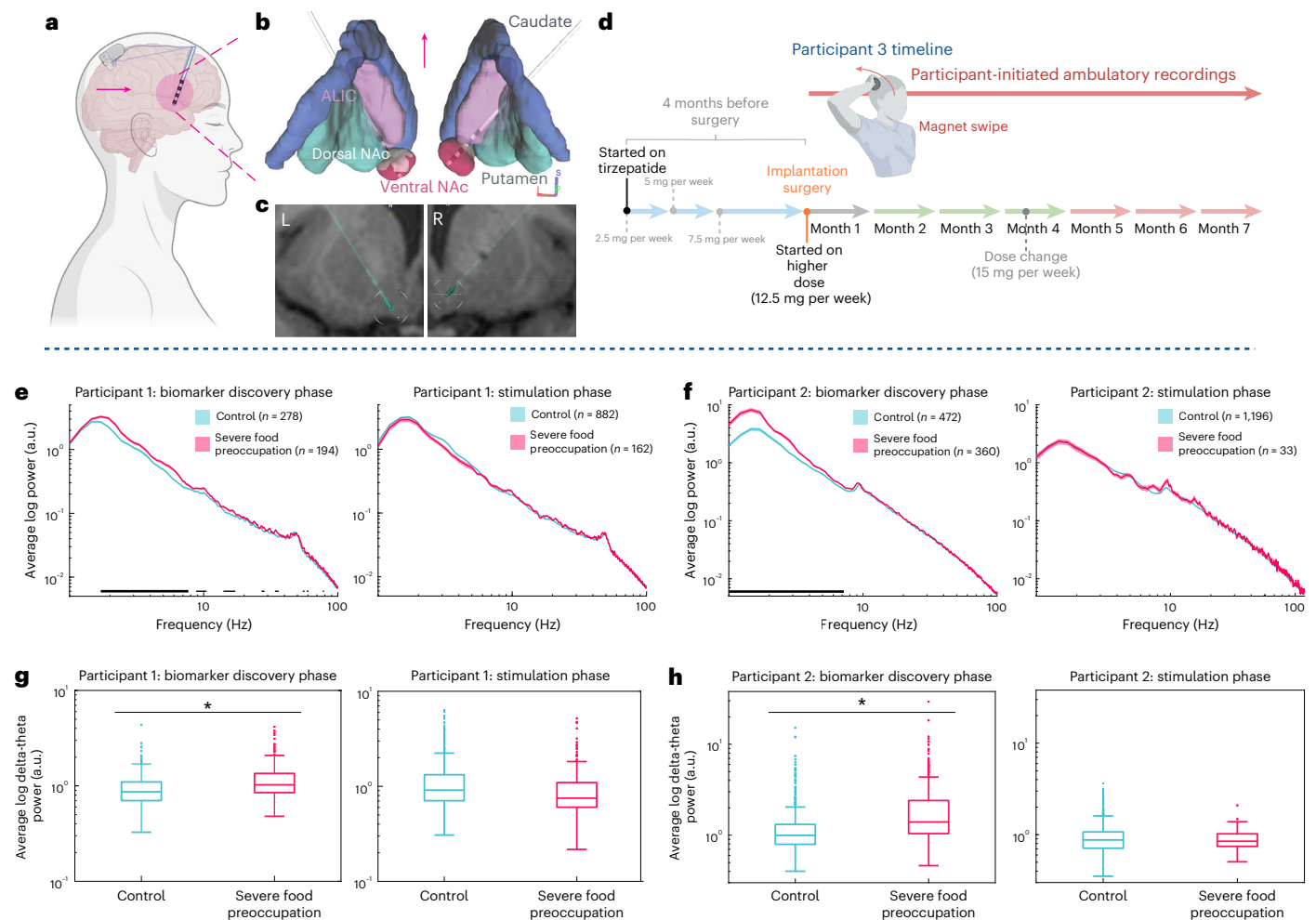


Fig. 1 | Background information of participant 3 and association of increased delta–theta power in the ventral NAC with severe food preoccupation in participants 1 and 2. **a**, Two quadripolar depth electrodes were placed bilaterally in the ventral NAC of participant 3 with a neurostimulator fully implanted subgaleally in the skull. **b**, Anatomical figure of participant 3 (view from posterior to anterior): three-dimensional rendering of DBS electrodes and their position in basal forebrain structures in the participant's native space: ventral NAC, magenta; dorsal NAC, white; putamen, green; caudate, blue; anterior limb of internal capsule (ALIC), light pink. **c**, Anatomical magnetic resonance imaging of participant 3 (Supplementary Fig. 1). L, left hemisphere; R, right hemisphere. Prior participants in this ongoing trial had similar electrode placement²¹. **d**, Timeline of crucial events for participant 3. A larger illustration and specifics for data collection and use are described in the Methods and Supplementary Fig. 2. **e**, Participant 1 (left ventral NAC): power spectrum (mean $\pm$ s.e.m.) during the biomarker discovery (left) and stimulation (right) phases when the participant was relaxing (control, blue) or in a severe food preoccupation state (pink). The bottom black lines indicate frequencies with statistically significant differences in power values between the control and severe food preoccupation conditions after two-sided permutation testing ($P < 0.05$) with cluster correction. **f**, Data from participant 2 (left ventral NAC), using the same format as in **e**. **g**, Participant 1 (left ventral NAC): delta–theta band (≤ 7 Hz) power during the biomarker discovery (left) and stimulation (right) phases when the participant was relaxing (control, blue) or in a severe food preoccupation state (pink). The center line of the box indicates the median; the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The individual points outside the whiskers are considered as outliers. The top black line with a single asterisk in the box plot shows statistically significant differences between two conditions after two-sided permutation testing ($*P < 0.05$). **h**, Data from participant 2 (left ventral NAC), using the same format as in **g**. For more information, including the right NAC, see Supplementary Fig. 3 and Supplementary Tables 1 and 2. Illustrations in **a** and **d** created using BioRender.com.

Our findings raise the possibility that this delta–theta band oscillation could serve as a target engagement biomarker, but its relationship to food preoccupation warrants more controlled investigation. Moreover, the phenomenon of a biomarker preceding actual behavioral change has been reported previously in the context of other behaviors relevant to psychiatric illness^{22,29}. Thus, the early findings reported in this study could provide the foundations of developing such a biomarker-based approach for tirzepatide administration for dysregulated eating, a strategy garnering interest for neuropsychiatric disorders^{30,31}. Although the invasive nature of monitoring this biomarker may limit scalability, the results reported in this study could inform preclinical studies given that the low-frequency nature of this biomarker is conserved at least when recorded from the NAC across

mouse and human studies²⁴. Further, noninvasive strategies can be developed to capture relevant brain dynamics; a parallel can be found in patients with Parkinson disease, where a prominent beta band signal has been detected both within the subthalamic nucleus and via scalp EEG^{32,33}. Thus, a biomarker-based approach holds promise as a strategy to optimize incretin-based therapies for food preoccupation^{18,19}. This study has some limitations. As this is a single uncontrolled case study, it is unknown whether the findings will generalize, for example, to other incretin-based therapies. Given the potential compulsive component in patients exhibiting dysregulated eating behaviors, the delta–theta biomarker may not be applicable to the broader population with obesity. In addition, we cannot determine whether the effects of tirzepatide are due to direct action in the NAC or identify which incretin

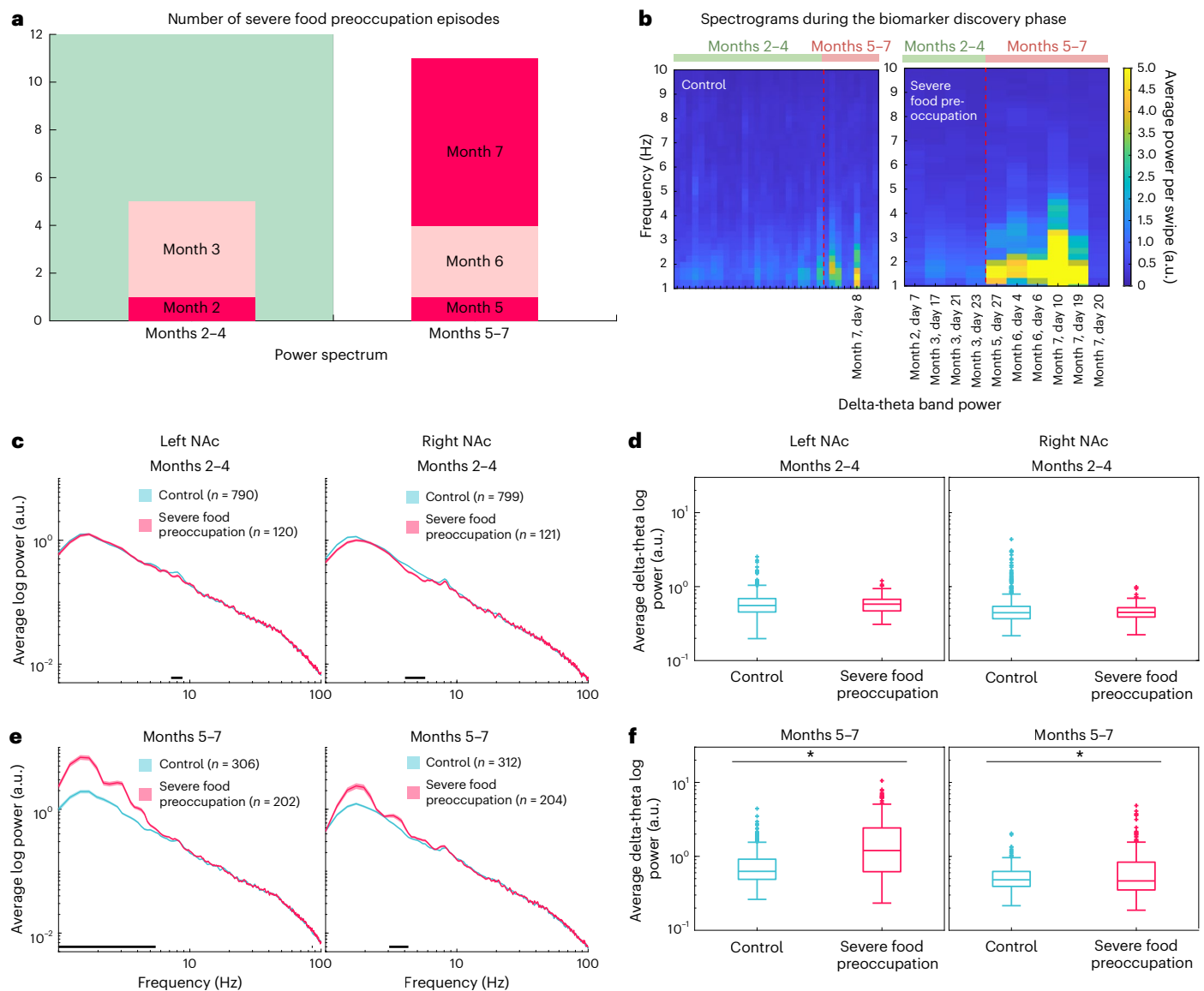


Fig. 2 | Association of increased delta-theta power in the ventral NAC with severe food preoccupation in participant 3. **a**, Number of severe food preoccupation episodes per month after surgery (excluding month 1 after surgery because of a potential implantation effect²⁷; month 4 had no episode). The green block denotes months 2–4. **b**, Participant 3 (left ventral NAC): spectrograms from magnet swipes for the control (left) and severe food preoccupation (right) conditions during the biomarker discovery phase (months 2–7). These spectrograms show power values per frequency from 1 to 10 Hz when the participant was relaxing (control; $n = 33$) or when the participant was in a severe food preoccupation state ($n = 10$). Each column corresponds to one magnet swipe episode, which is a participant-triggered iEEG recording (90 or 180 s). The red dashed line denotes the end of month 4 and the beginning of month 5 (see the green and pink bars above each spectrogram). For the results from the right ventral NAC, see Supplementary Fig. 5. Note that the apparent similarity in the number of severe food preoccupation episodes across months 2–4 versus months 5–7 arises from technical limitations (for example, device storage or trigger failure). Data reflect the number of available electrophysiological recordings. During months 2–4, the reported number of severe food preoccupation episodes was five but only four iEEG data were

available, as shown on the right (under the green bar). Likewise, during months 5–7, the reported number was 11 but only six iEEG recordings were collected, as shown on the right (under the pink bar). **c,d**, Participant 3 (ventral NAC): power spectrum (mean $\pm$ s.e.m.) (**c**) and delta-theta band (≤ 7 Hz) power (**d**) when the participant was relaxing (control, blue) or in a severe food preoccupation state (pink) during months 2–4. **c**, The bottom black line shows statistically significant differences in power values between the control and severe food preoccupation (two-sided permutation testing ($P < 0.05$) conditions with cluster correction). There was no significant difference except at 7.2–8.8 Hz where the power value from severe food preoccupation was lower than the control. **d**, The center line of the box indicates the median; the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The individual points outside the whiskers are considered as outliers. The top black line with a single asterisk shows statistically significant differences between two conditions after two-sided permutation testing ($*P < 0.05$). During months 2–4, there was also a 7% decrease in body weight relative to the baseline before surgery (138–128 kg; Supplementary Fig. 6). **e,f**, Power spectrum (mean $\pm$ s.e.m.) (**e**) and delta-theta band (≤ 7 Hz) power (**f**) from months 5–7, formatted as in **c,d**. **c–f**, For more information, see Supplementary Table 3.

receptor is involved (that is, GLP-1 or GIP). Lastly, analyzing electrophysiological data in the absence of tirzepatide use was not feasible, as it was part of the ongoing diabetes management of participant 3. Thus, the possibility that the observed electrophysiological changes may be

attributable to other confounding factors (for example, postoperative recovery, elapsed time since surgery or unrelated behavioral changes) cannot be excluded. Discontinuation of tirzepatide could pose both clinical and ethical challenges, but future studies may be designed to

directly investigate the physiological impact of incretin-based therapies on brain reward circuitry.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgments, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-025-04035-5>.

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Methods

Written informed consent was obtained from participant 3 to participate in an early feasibility trial of ‘responsive deep brain stimulation (rDBS) for patients with treatment-refractory obesity and loss-of-control eating’ (ClinicalTrials.gov registration [NCT03868670](#))²³. This trial was approved by the U.S. Food and Drug Administration (FDA) and the institutional review board (IRB) of the University of Pennsylvania (IRB no. 850489 and investigational device exemption no. G180079).

Participants

Participant 1 is a 51-year-old woman with severe treatment-resistant obesity (body mass index (BMI) = 46.5 kg m⁻²) and distressing food preoccupation despite bariatric surgery. After Roux-en-Y gastric bypass surgery, she lost 52.16 kg but she gradually regained the weight, returning to her before surgery weight at the time of enrollment. She had the comorbidities of neoplasm, lower back pain, kyphoscoliosis/scoliosis, hypertension, esophageal reflux, dyslipidemia, complicated migraine and anxiety at the time of enrollment.

Participant 2 is a 61-year-old woman with severe treatment-resistant obesity (BMI = 47.1 kg m⁻²) and distressing food preoccupation despite bariatric surgery. After Roux-en-Y gastric bypass surgery, she lost 68.95 kg but regained the weight and was back to within 9% of her before surgery weight at the time of enrollment. She had the comorbidity of migraine at the time of enrollment. After bariatric surgery and before the enrollment, both participants tried many other weight loss strategies, including behavior therapy, support groups and medication, which were unsuccessful.

Both participants reported severe food preoccupations particularly related to emotional-related and stress-related triggers that often led to loss-of-control eating episodes (approximately five episodes per week and four episodes per week, respectively, as measured using the Eating Disorder Examination³⁴). Neither participants reported previous testing or diagnosis regarding monogenic obesity, which is not part of our clinical standard. These participants were enrolled at Stanford University and the study was approved by Stanford University’s IRB (IRB no. 46563) at that time. Informed consent was obtained from both participants (please refer to ref. 21 for more details).

Participant 3 is a 60-year-old woman with severe treatment-resistant obesity (BMI = 46.1 kg m⁻²) despite bariatric surgery and comorbid type 2 diabetes. She did not report any previous testing or diagnosis regarding monogenic obesity. She presented to us reporting substantial distress from food preoccupation. Her frequent food preoccupations led to unwanted eating behaviors, including many loss-of-control eating episodes. Before laparoscopic Roux-en-Y gastric bypass surgery, she weighed 154 kg and she had cravings for calorically dense food choices. After her bariatric surgery, she reached a nadir weight of 115 kg (BMI = 38.7 kg m⁻²), but near the time of enrollment, her weight had increased to 137 kg (BMI = 46.1 kg m⁻²). She stated that she was often preoccupied with thoughts of food, which led to ordering a meal out or to continual snacking, even though she wanted to resist. Her preoccupation focused on both sweet and salty foods, such as prepackaged cupcakes and roast beef sandwiches with french fries. She reported 19 loss-of-control episodes in the previous month on study entry. The participant endorsed eating until uncomfortably full, eating large amounts when she was not hungry and feeling guilty after these episodes, with high levels of distress associated with them.

The participant fulfilled all eligibility criteria of the trial, which are mainly: (1) BMI = 40–60 kg m⁻²; (2) unsuccessful intervention with bariatric surgery, behavioral therapy and pharmacological therapy for dysregulated eating behavior and weight loss and (3) loss-of-control eating episodes at least four times per week. Importantly, these included unsuccessful use of a GLP-1 receptor agonist (dulaglutide), which resulted in no relief in her weight or food preoccupation. She was switched to a GLP-1-GIP dual receptor agonist (tirzepatide) for

its FDA-approved indication treating type 2 diabetes. There was no reported impact on weight and food preoccupation at 7.5 mg per week of tirzepatide at the time of baseline assessment. She reported temporary weight loss followed by subsequent return to her initial weight with no reported impact to her food preoccupation and loss-of-control eating episodes. As this agent was intended for treating her type 2 diabetes, the participant was enrolled into the study and underwent implantation of the rDBS system (NeuroPace) bilaterally in the NAc. The patient increased the tirzepatide dose to optimize her diabetes management as suggested by the clinical team given the known risk of this medical comorbidity on surgical outcomes, particularly infection, given the medical device implantation. At the time of implantation, the patient was receiving 12.5 mg per week and it was further increased to 15 mg per week after approximately 4 months for continued optimization of glucose control. She had comorbidities of hypertension, hyperlipidemia, coronary artery disease, nonalcoholic steatohepatitis, irritable bowel, migraine and asthma at the time of enrollment.

Surgical procedure

The surgical procedure has been reported previously^{23,35}. Briefly, probabilistic tractography was used to guide surgical targeting of the NAc as described previously³⁶. On the day of surgery, implantation of bilateral DBS electrodes in the NAc was performed under awake conditions as per our standard institutional practice. Using a personalized appetitive provocation task, microelectrode recording was performed intraoperatively to identify single-unit or multiunit appetitive neural activity³⁵. After confirmation of the target with electrophysiology and imaging, a quadripolar depth electrode was placed and macroelectrode monopolar stimulation mapping was conducted to confirm positive effects and no adverse effects. After securing the DBS electrodes, the electrodes were connected to the neurostimulator pulse generator, which was placed in the right parietal skull region of the patient.

Data acquisition

iEEG recordings were acquired from the FDA-approved rDBS device (NeuroPace) as reported previously²¹. An rDBS device is different from a regular DBS device in that it stimulates only when it detects a predefined biomarker rather than stimulating continuously. Neural recordings acquired from the rDBS device were used to identify biomarkers differentiating severe food preoccupation swipes from control swipes. iEEG data were recorded at a 250-Hz sampling rate and bipolar re-referenced online. We used data from channels 1 and 3, which were referred to as the data from the left and right ventral NAc in this article. Four electrode contacts were located in the following order: (1) ventral NAc (the most ventral contact; presumed NAc shell³⁶); (2) dorsal NAc (presumed NAc core³⁶); (3) and (4) ALIC. For all participants, an electrode in the left hemisphere, one channel (channel 1) was bipolar re-referenced between contacts 1 and 3; the other channel (channel 2) was between contacts 2 and 4. Likewise, an electrode in the right hemisphere, one channel (channel 3) was bipolar re-referenced between contacts 1 and 3, and the other channel (channel 4) was between contacts 2 and 4.

The biomarker discovery phase data of participants 1 and 2 overlaps with ambulatory data used in our previous report²¹. However, the focus and analytical approach in the previous report were fundamentally different from the current study. In the previous report, the analysis was centered around pure ‘craving’ in the absence of hunger, aiming to dissociate hedonic and homeostatic eating by stratifying data based on ‘craving’ and ‘hunger’ ratings. This allowed us to explore the NAc electrophysiology in states seemingly dominated by hedonic versus homeostatic derives, given that we were performing biomarker discovery to guide an rDBS. Thus, we hypothesized that stimulation would be more behaviorally specific to hedonic states.

However, in the current report, we focused on a distinct construct, that is, food preoccupation, as defined by ‘heightened and/or persistent

reactivity to food cues¹¹. This encompasses a broader range of influences, including hunger and other sensorial, environmental and social cues¹¹. The excessive food preoccupation observed in our participants reflected combined alterations in both homeostatic and hedonic eating rather than hedonic eating alone¹. To better align with this conceptual shift, data were stratified to ‘severe food preoccupation’ only using the craving rating regardless of the hunger rating. This stratification included episodes with both high craving and hunger ratings.

For participants 1 and 2, the bipolar reference montage was adjusted during early recording period and the stimulation safety testing period. We confined our analysis to the periods across all participants when the same recording montage was used. Thus, the biomarker discovery phase used for participant 1 was limited to data collected for approximately 1 month before final initiation of stimulation, which took place during months 8–9 after surgery. There was no apparent change in food preoccupation during this brief period of safety testing. To examine the effect of stimulation, we used a dataset collected from the moment immediately after the stimulation parameter had been set to a maximum dose to month 18 after surgery (that is, the stimulation phase). To reduce confounders to our electrophysiological analysis due to stimulation, we used magnet swipes that had no stimulation within the magnet swipe time window. The same was done for participant 2.

For participant 2, we defined the period from when electrophysiology data were collected between month 3 and month 6 after surgery before stimulation initiation as the ‘biomarker discovery phase’. To examine the effect of stimulation, we again used a dataset collected from the moment immediately after the stimulation parameter had been set to a maximum dose to month 18 after surgery (that is, the stimulation phase).

For participant 3, stimulation was not delivered throughout the data acquisition reported in this article. Moreover, we excluded data from up to a month from the surgery date (month 1) because of confounding with an implantation effect, as we did for the prior participants, although implantation effects typically last less than a month in patients with Parkinson disease²⁷. Thus, months 2–7 corresponded to the ‘biomarker discovery phase’. We limited this case study’s interim analysis to the 6-month recording phase planned by the investigational device exemption trial to avoid further trial-related confounders.

Magnet swipe (ambulatory iEEG recordings). With the rDBS system, participants can initiate iEEG recordings by swiping their magnet over the surgically implanted device under the scalp (Supplementary Fig. 2). The magnet swipe triggers the iEEG recordings, which record a preset length of time before and after the magnet swipe with a two-to-one ratio. For instance, if the preset length is 90 s, it records 60 s before the magnet swipe and 30 s after it. For this study, the length was set to 90 s (participants 2 and 3) or 180 s (participants 1 and 3).

For the control condition of participants 1 and 2, data were automatically recorded at a preset time (12:00 for participant 1 and 17:00 for participant 2), the time participants answered that they were most likely to be at rest. This was to reduce their study burdens. For participant 3, the control condition consisted of magnet swipes collected when she was relaxing and not feeling food cravings. For control episodes from scheduled recordings, we removed them if craving swipes were present near the scheduled recording time.

For the food preoccupation condition, we asked participants to swipe the magnet when they felt cravings for food and before eating. Considering food preoccupation as ‘heightened or persistent reactivity to food cues’, we focused on the extent of food preoccupation regardless of hunger level, unlike our prior report²¹, because cues that could elicit food preoccupation include not only hunger and craving but also other sensorial, environmental and social aspects¹¹. We asked participants to swipe when they were feeling a sense of craving to capture the most relevant moment of food preoccupation. For all magnet swipes, participants were asked to keep a magnet swipe diary, recording their

craving, hunger and thirst levels, the extent they felt a loss of control and the extent they felt compelled to eat in a 5-point Likert scale (1 for none/not at all versus 5 for extreme/extremely). Therefore, magnet swipes with intense craving were classified as severe food preoccupation based on craving ratings per participant.

Behavioral data. We collected participants’ number of severe food preoccupation episodes per month through the magnet swipe diary but used ecological momentary assessment or verbal or written reports as a supplement if they forgot to keep them in the diary.

Signal processing

In the offline analysis, standard preprocessing techniques were conducted in MATLAB (v.R2022b) using the FieldTrip Toolbox³⁷, which involved the application of a 1–124-Hz band-pass filter. Static spectral analysis was performed using a multi-taper method with four Slepian multi-tapers per epoch. These epochs were acquired using chunking magnet swipes every 5 s without overlaps. A full power spectrum (1–124 Hz) was acquired with 0.5-Hz frequency resolution; delta–theta band powers were acquired using a ≤ 7 -Hz window. Epochs containing artifacts were removed if the artifact was larger than the six standard deviations of the data points of a corresponding magnet swipe. For the power spectrums in Fig. 2b, power values per frequency were averaged per a magnet swipe.

Statistical testing

Power spectral density values from the control and severe food preoccupation swipes were tested using two-sided permutation testing with 1,000 permutations and $P = 0.05$. Then, it underwent cluster correction using a cluster size threshold of the top 2.5%. Delta–theta band power values from two swipe conditions were tested using two-sided permutation testing with 10,000 permutations and $P = 0.05$.

Transition point detection differentiating months 2–4 and months 5–7

The transition point, which was predefined based on the emergence of the biomarker, was further validated using a model that identifies the transition point corresponding to the most pronounced change in power values within the delta–theta frequency band (≤ 7 Hz)^{25,26}. More specifically, the transition point between two periods was determined by minimizing the total residual error, calculated from deviations of each time point from the root mean square estimate of the period to which it belongs.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data that support the findings of the present study are available from the corresponding author (C.H.H.) upon reasonable request. The data are not yet publicly available because they contain information that could compromise research participant privacy and consent. As this study is part of an ongoing clinical trial, enrolling additional participants (ClinicalTrials.gov registration no. NCT03868670), all data will be deposited in the Data Archive Brain Initiative (<https://dabi.loni.usc.edu>) as part of the BRAIN Initiative on completion of the study. During this time, any request will be reviewed in a timely manner by the corresponding author, corresponding author’s institution and ultimately shared within reason of a signed data transfer agreement.

Code availability

All code has been made publicly available and can be found on GitHub at https://github.com/Wonkyung-Woni-Choi/Tirzepatide_Case_Report/tree/main.

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Author contributions

W.C., Y.-H.N., L.Q., K.W.S. and C.H.H. wrote the paper with invaluable input from all authors. W.C., A.C., G.C., W.B.W., D. Bakalov, N.F., G.M. and K.C.A. conducted the clinical and electrophysiological data collection. U.T., D. Batista and N.S. provided technical support for data collection. N.F., M.K., D.J. and G.M. provided regulatory support for conducting the clinical trial. R.L.S., A.A., M.R.H., I.C., M.C., K.C.A., K.W.S., T.A.W. and C.H.H. provided clinical guidance throughout the study. Y.-H.N., B.P., J.I.G., T.A.W. and C.H.H. provided scientific guidance throughout the study. W.C. conducted the data analysis under the guidance of Y.-H.N., B.P. and K.W.S. L.Q. and C.H.H.

performed the surgical procedure. C.H.H. provided supervision and guidance throughout the study and provided financial support.

Competing interests

No funding from NeuroPace was received for the present study nor when the data analyses reported in this study were conducted by NeuroPace employees. W.C., Y.-H.N., K.W.S. and C.H.H. filed a provisional patent application related to sensing accumbens activity to guide the treatment of obesity and related disorders. The laboratory of M.R.H. at the University of Pennsylvania receives research funding from Boehringer Ingelheim, Eli Lilly and Company, Pfizer, Gila Therapeutics and Coronation Bio, which was not used to support these studies. M.R.H. is a founding scientist of Coronation Bio, a Delaware corporation that pursues biological work unrelated to the current study. K.C.A. receives research funding from Novo Nordisk for a project that is unrelated to the scope of this study. A.A. receives research funding from Eli Lilly and Company, Novo Nordisk, Fractyl Laboratories and Altimmune, which was not used in support of these studies. A.A. received consultant honoraria from Novo Nordisk and CVS Caremark, which is unrelated to the current study. I.C. received teaching honoraria from Medtronic, research funding from Boston Scientific and research support from Precision Neuroscience, which are unrelated to the scope of this study. K.W.S. received a consultant honorarium from Johnson & Johnson, which is unrelated to the current study. T.A.W. has received research support from Novo Nordisk and Eli Lilly for projects unrelated to the current study. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-025-04035-5>.

Correspondence and requests for materials should be addressed to Casey H. Halpern.

Peer review information *Nature Medicine* thanks Louis Aronne, Carina Oehrns and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Jerome Staal, in collaboration with the *Nature Medicine* team.

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Software and code

Policy information about [availability of computer code](#)

Data collection	Electrophysiologic data was obtained from intracranially placed depth leads by using commercially available NeuroPace RNS system
Data analysis	All data analyses were performed in MATLAB (R2022b) using custom scripts built upon the FieldTrip Toolbox (FieldTrip Toolbox-20221118; https://www.fieldtriptoolbox.org/). The electrode artifacts from the co-registered post-operative CT, together with the pre-operative MRI, and atlas-based regions of interest were then loaded in DSI studio for 3D rendering (http://dsi-studio.labsolver.org/). The pre-operative MRI anatomical images were co-registered to post-surgical CT scan using Advanced Normalization Tools (ANTs) for electrode localization.

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The data that support the findings of this study are available upon reasonable request to the corresponding author [CHH]. The data are not publicly available due to

them containing information that could compromise research participant privacy/consent. As this is part of an ongoing clinical trial, enrolling additional subjects (Trial registration # NCT03868670), all data and code will be deposited into Data Archive Brain Initiative (<http://dabi.loni.usc.edu>) as part of the BRAIN initiative at the completion of the study. During this time, any request will be reviewed in a timely manner by the corresponding author, corresponding author's institution, and ultimately shared within reason of a signed data transfer agreement.

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Reporting on sex and gender

All participants in the study were female in both sex and gender, based on self-report. Although the study was not designed to be limited to a specific sex, and the study team believes the findings are not sex-specific, we currently do not have male participants to support this claim.

Reporting on race, ethnicity, or other socially relevant groupings

We did not use socially constructed categorization variable.

Population characteristics

Participant information is described fully in detail in the Methods section.

Recruitment

Participants 1 and 2 were recruited at Stanford through the Stanford Bariatric Clinic, newspaper advertisements (print and online), Facebook, and ResearchMatch. Participant 3 was recruited at the University of Pennsylvania through the site's bariatric program, Meta advertisements, iConnect (UPenn's patient recruitment management system), and email blasts targeting potentially eligible individuals. Participant bias is present due to the use of self-reported behavioral data. Additionally, recruitment-related bias may be present, as individuals who responded to the study advertisements were likely those who perceived their symptom severity to be significant enough to warrant consideration of an invasive intervention.

Ethics oversight

Written informed consent was obtained from all participants for enrollment in an early feasibility trial of "responsive deep brain stimulation (rDBS) for patients with treatment-refractory obesity and loss of control (LOC) eating" (ClinicalTrials.gov Identifier: NCT03868670). The trial received approval from the U.S. Food and Drug Administration (FDA) and the Institutional Review Board (IRB) at the University of Pennsylvania (Penn IRB #850489; Investigational Device Exemption [IDE] #G180079). Participants 1 and 2 were initially enrolled at Stanford University, where the study was approved by Stanford's IRB (IRB #46563), prior to the main study site being transferred to the University of Pennsylvania.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

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Sample size

This is a n=1 case study that references preliminary findings from two previously enrolled participants. All three participants are part of an ongoing clinical trial with a target enrollment of six participants (N=6). No formal sample size calculation was performed. Given that this is a case study, data from a single participant (Participant 3) is considered sufficient for the purposes of this report.

Data exclusions

No data relevant to the case report was excluded.

Replication

A delta-theta band signal in the nucleus accumbens (NAc) was observed in all three participants during the Biomarker Discovery phase.

Randomization

For Participant 3, the data were not randomized. For Participants 1 and 2, although Participant 1 was randomized to a sham condition and Participant 2 to an active stimulation condition during a two-month safety testing phase following the recording phase (as per the FDA-approved protocol), this randomization is not relevant to the current case report.

Blinding

No blinding was conducted for Participant 3. While Participants 1 and 2 were blinded during the two-month safety testing phase, the blinding is not relevant to the current case report, which does not address stimulation efficacy.

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☒	☐ ChIP-seq
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Clinical trial registration	ClinicalTrials.gov Identifier: NCT03868670
Study protocol	The study protocol can be found here: https://doi.org/10.1093/neuros/nyaa300
Data collection	Data collection and analysis spanned from January 2020 to August 2025, covering all three participants. Data were collected at Stanford University for Participants 1 and 2, and the University of Pennsylvania for Participant 3, with magnet swipes and self-reported ratings completed by participants at home.
Outcomes	Primary and secondary outcome variables were defined in the clinical trial protocol. However, this case report focuses on examining the association between tirzepatide use and changes in Participant 3's food preoccupation and electrophysiological changes—analyses that are not directly related to the primary objectives of the clinical trial.

Plants

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