The need to connect: Acute social isolation causes neural craving responses similar to hunger.

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Abstract

When people are forced to be isolated from one another, do they crave social interactions in the same way a hungry person craves food? To address this question, we used functional magnetic resonance imaging (fMRI) to measure neural responses in participants (n=40) evoked by food and social cues after ten hours of mandated fasting or total social isolation. After isolation, people felt lonely and craved social interaction. Midbrain regions showed increased activation to food cues after fasting and to social cues after isolation; these responses were correlated with self-reported craving. Neural patterns in response to food cues when participants were hungry generalized to social cues after isolation. Our results support the intuitive idea that acute isolation causes social craving, similar to hunger.

Keywords: social isolation, social motivation, social craving, food fasting, fMRI, midbrain, substantia nigra, ventral tegmental area

How are people affected by a period of forced social isolation? Chronic social isolation and loneliness are associated with lower physical(*1-5*) and mental(*5-9*) health, but little is known about the consequences of acute mandatory isolation. Positive social interactions in and of themselves may be basic human needs, analogous to other basic needs like food consumption or sleep(*10-12*). If so, the absence of positive social interaction may create a want, or "craving", that motivates behavior to repair what is lacking(*10*). Cues associated with positive social interaction (e.g., smiling faces) activate neural reward systems(*13, for review*). However, research on the neural representation of *unmet* human social needs is lacking(*14*).

In the brain, motivation – i.e., the sensation of "wanting" something(*15, 16*) - has been consistently linked with dopamine (DA) transmission in the so-called "brain reward circuit"(*17, 18*). The core brain areas of this reward circuit comprise the dopaminergic midbrain (with most midbrain DA neurons residing in substantia nigra (SN) pars compacta and ventral tegmental area (VTA)(*19, 20*)) and the striatum(*15, 17, 21-25*). In both animals and humans, the dopaminergic reward circuit is triggered by unexpected rewards, which lead to phasic firing of DA releasing neurons in the midbrain(*19, 20*). Neural activity in midbrain and striatum is associated with the sensation of "wanting" or "craving" in humans(*15, 26, 27*), particularly in response to images of food when hungry, and to drug-related images in people who are addicted(*28-30*).

In social animals, social interactions act as primary rewards(*31-34*): they are inherently pleasurable and motivate behavior in the absence of any other reward. Rodents, for example, spontaneously seek social contact(*35*), fare better in group housing than in isolated housing(*35, 36*) and cooperate with and help cagemates(*37-40*). Extended periods of isolation, especially during development, can dramatically disrupt behavior and brain function(*41, 42*). Even a brief acute period of social isolation in rodents induces an increased motivation for subsequent social interaction(*43*). This increased sociability depends on midbrain DA neurons(*44*), similar to other kinds of craving(*45, for review*). After 24 hours of isolation, DA neurons of the midbrain dorsal raphe nucleus (DRN) are activated when the mice seek social interaction. Optogenetic activation of DRN DA neurons increases post-isolation sociability, and deactivation reduces post-isolation sociability, especially in socially dominant mice. Importantly, DRN activity is not inherently pleasant (and thus is unlikely to reflect reward anticipation): mice learn to avoid novel places where these neurons are stimulated. Thus, DRN DA neurons in mice appear to encode an aversive "loneliness-like" state that motivates social engagement(*44*). However, the

homology to human loneliness has been disputed(*14*), and it is not possible to assess whether a mouse subjectively feels lonely.

In sum, the intuitive idea that unmet social needs evoke a motivation to seek social interaction, analogous to the way hunger motivates people to seek food, has never been directly tested in humans. Would acute social isolation evoke a "social craving" response in dopaminergic midbrain regions in humans? To address this question, we had to first address three methodological challenges.

First, could we experimentally induce the experience of social isolation in human participants? To differentiate between pre-existing individual differences and the direct effects of isolation, we needed to induce isolation experimentally in a within-subject design, similar to the experimental studies of rodents(*43, 46*). However, human loneliness is not a simple product of objective isolation: people can be alone without feeling lonely, or feel lonely even in a crowd(*47*). Moreover, experimentally induced isolation would necessarily be brief, relative to the human lifespan, and for ethical reasons, human participants (unlike rodents) would be able to predict when the isolation would end. In all, the first challenge of this research was to develop an experimental induction of objective isolation that created the subjective experience of unmet social needs in human participants. To address this challenge, we had socially-connected healthy human adults spend ten hours (9 am to 7 pm) alone, with no social interaction and no other social stimulation (e.g. social media, email, fiction). We used self-report questionnaires to assess people's resulting subjective experience of loneliness and social craving.

Second, could we measure neural responses in the relevant dopaminergic midbrain regions? In primates, aversive motivation is represented in the substantia nigra pars compacta and ventral tegmental area (SN/VTA)(*23*), and SN/VTA is activated by craving for food and for drugs of addiction(*28-30*). We therefore hypothesized that acute isolation in humans might produce a social craving response in SN/VTA. Neuroimaging of the SN/VTA poses a technical challenge, though, because it is a small structure, adjacent to the sphenoid sinus (a large, air-filled cavity located anterior to the brainstem) and therefore prone to distortions and signal loss(*19, 20*). To address this challenge, we optimized MRI image acquisition parameters, and used a newly developed atlas(*48*) to identify SN/VTA in individual participants' brains.

Third, could we measure signals associated with craving? Although fMRI cannot directly measure DA levels, blood oxygenation dependent (BOLD) signals recorded in midbrain are correlated with DA

levels(*19, 49*). In the substantia nigra in particular, ~70% of the neurons are dopaminergic, so fMRI signals in this brain area likely mainly reflect DA neuron activity(*20, for review*). To address this challenge, we employed two strategies: first, we developed a cue-induced craving paradigm, in which participants viewed pictures of their favourite social activities, favourite foods, and a pleasant baseline (flowers). We included favourite foods so that we could compare social craving, within participants, to a well-established neural craving response, evoked by viewing food cues after several hours of fasting(*29, for review*). Second, we included an independent functional localizer task to identify voxels in each participant's midbrain that are maximally sensitive to expected reward and novelty, consistent with DA activity(*15*). We then tested for responses to social cues after isolation, in these voxels in particular.

In summary, we measured the subjective (self-reported craving) and neural (midbrain activation) response to food and social cues, following fasting and following acute social isolation. We predicted that SN/VTA would show higher BOLD activity in response food cues after fasting and to social cues after acute isolation. These neural responses should be correlated with the intensity of subjective craving, and thus might reflect individual differences in social connectedness and/or loneliness. Furthermore, we predicted that social craving and food craving share a common neural signature in SN/VTA, and therefore expected that a classifier trained on SN/VTA response patterns during food craving would generalize to classify patterns during social craving. Lastly, because the striatum is a major target of projections from midbrain neurons and their firing results in increased DA transmission in the striatum(*18, 50, 51*), we expected to see the same pattern of results in the striatum, i.e.: increased activation to food cues after food deprivation and to social cues after social isolation. All predictions and methods were preregistered on the Open Science Framework (https://osf.io/cwg9e/).

Methods

Participants

Participants (n =40) were healthy right-handed adults, ranging in age from 18-40 years (mean age 26 years; N=27 female). An a priori power analysis in G*Power 3.0(*52*) targeted on the detection of medium effects (d=0.5, α=0.05 and 1-β=0.80) suggested a sample size of n=34. The targeted effect size was chosen based on findings from studies employing cue-induced craving paradigms for drug craving(*53*), food cravings(*28, 54-56*) and internet gaming craving(*30*) which report medium to large effect sizes in cue reactivity(*53*). We performed power calculations for medium effects because social

craving might be less intense or more variable than cue reactivity in drug craving and food craving. We therefore recruited 42 participants to account for potential attrition or exclusion for MRI data quality; two participants were unable to complete all experimental sessions and so were dropped from analysis, leaving 40 complete datasets.

Participants were recruited via e-mail lists and through online advertisements and flyers. Interested individuals filled out a screening questionnaire to assess eligibility for the study. People were eligible if they reported a healthy Body Mass Index (BMI: 16-30), no current calorie restricting diet, no permanently implanted metal in their body, no history of brain damage, and no currently diagnosed mental health disorder or substance abuse. Because we aimed to study social motivation in a sample of adults who have frequent and regular social interactions, we also excluded people who i) lived alone, ii) reported current feelings of loneliness on the UCLA Loneliness Scale(*57*) (i.e., we excluded people with scores above 50, which is one standard deviation above the mean for a student sample(*57*)); or iii) reported smaller social network sizes than typically expected of adults(*58*) according to a social network size measure(*59*) and the Social Support Questionnaire(*60*) (i.e., we excluded people with social networks 2 or more SD below mean, based on prior measured distributions from Von der Heide et al. 2014(*61*)). All experimental procedures were approved by MIT's institutional review board, COUHES (couhes.mit.edu). Participants signed a consent form describing all experimental procedures before participating in the study. Each participant was compensated with $350 for participating in three fMRI sessions and completing the 10 hours of food fasting and 10 hours of social isolation.

Experimental Procedures

Each participant was scanned in three fMRI sessions, separated by at least 24 hours. Figure 1 shows an overview of the experimental procedures. One session followed 10 hours of food fasting; one session followed 10 hours of social isolation, and one session was a baseline without any mandated prior abstinence. Between participants, the order of sessions was counterbalanced; each participant was pseudo-randomly assigned to one of the possible orders of the three different sessions with the restriction that all 6 possible sequences were approximately equally likely in the full sample.

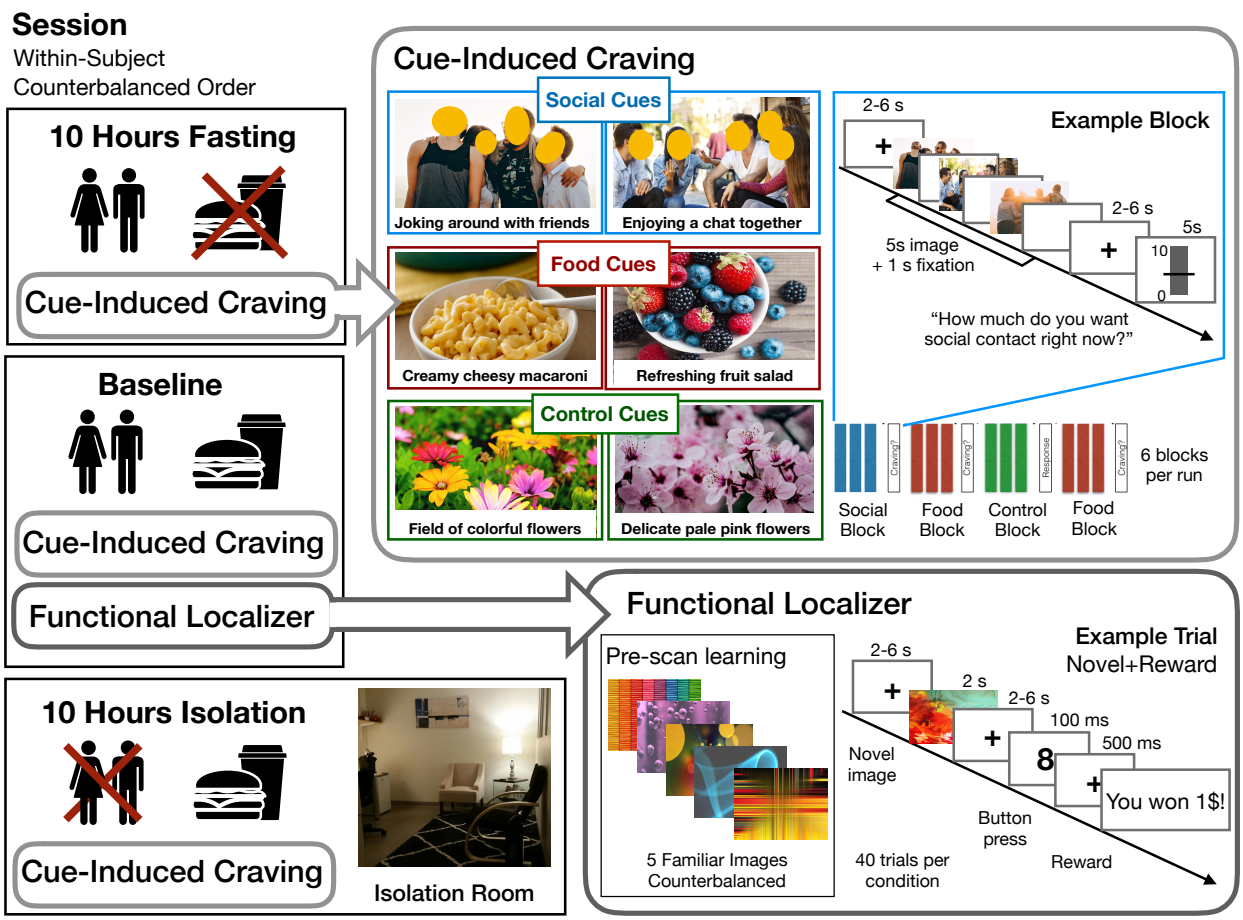

Figure 1. Overview of the experimental procedures. Each participant underwent 3 experimental sessions: fasting, baseline and isolation (the order of sessions was counterbalanced across participants) and subsequently an MRI scan with the Cue-Induced Craving task. On the baseline day, participants also underwent a functional localizer task. Cue-Induced Craving task: Participants saw cues for social contact, food and control cues depicting flowers. (Note faces have been obscured in figure to comply with biorxiv policy). After each block of cues (showing 3 images), participants rated their self-reported social craving (after social blocks), food craving (after food blocks) and how much they liked the flower pictures (after control blocks). Functional Localizer: Participants memorized a set of 5 images prior to the scan (4 different sets of images were counterbalanced across participants). Immediately before the localizer task, participants were shown the memorized pictures again. During the task, participants saw either one of the memorized pictures or a novel picture indicating whether they would be able to win money or not.

Food fasting. Participants were asked to abstain from consuming any food or drinks/coffee (except water) for 10 hours before the fMRI session. We scheduled each fMRI session at 7pm in the evening; thus, participants were asked to refrain from eating after 9am on the day of the fasting session. We also asked participants to abstain from all forms of exercising on the day of food fasting in order to avoid exhaustion. Participants filled out an online questionnaire, rating their momentary food craving,

hunger, discomfort, happiness and dislike of fasting (on a visual analog scale (VAS) anchored at 0 (not at all) to 100 (extremely)), every two hours during the food fasting period.

Social isolation. Participants were socially isolated for 10 hours. On the day of the isolation session, participants arrived at the McGovern Institute for Brain Research, MIT building 46, at 8.15am. Because we aimed to keep all social interactions between the social isolation and the fMRI scan to a minimum, participants were given extensive instructions about the paradigm and MRI session, and a mock scanner session, before starting social isolation. Subsequently, participants gave their phones and laptops to the experimenter and were guided to a room containing an armchair, a desk and office chair, and a fridge with a selection of food, snacks and beverages. Participants remained in that room from 9am until 7pm. Participants were provided with a laptop (with parental controls enabled), allowing them to visit only our Slack channel (i.e., an online messenger software allowing communication between a group of people [www.slack.com]) and the webpage containing our online questionnaire. Messaging in Slack was restricted to informing participants about the arrival of food delivery and for emergencies (i.e., in case participants ran into problems which required assistance from the research team during isolation). Participants filled out an online questionnaire rating their momentary social craving, loneliness, discomfort, happiness and how much they disliked isolation (VAS anchored at 0 (not at all) to 100 (extremely)) every two hours during the social isolation period.

In advance of the session, participants were invited to send us text documents (without any social content) to read or work on during isolation; approved documents were printed or transferred to the provided laptop. In addition, we provided puzzles, Sudoku, coloring pages, non-social games (e.g., Tetris, Bubble Shooter, etc.) and drawing/writing supplies. The fMRI session was conducted immediately after the social isolation.

Baseline. Participants came into the lab at 7pm and completed the same fMRI tasks as in the other two conditions (in addition to a functional localizer task, see below). Participants were asked to not be hungry at the time of the scan.

fMRI

Participants were in the scanner for around 1 hour in each session. We started with anatomical scanning. For each participant, structural whole-head T2*-weighted structural images were collected in 176 interleaved sagittal slices with 1 mm isotropic voxels (FOV: 256 mm). In addition, whole-head T1-weighted structural images in 176 interleaved sagittal slices with 1 mm isotropic voxels (FOV: 256 mm) were collected. The T2* weighted anatomical scan was collected for anatomical identification of midbrain nuclei (i.e., the high content of iron in SN/VTA and red nucleus makes the T2* shorter and

darker in these areas (*19, 20*)). We confirmed the identification of mid-brain structures by registering to the newly available atlas of subcortical nuclei from Pauli et al. (*48*) and defined separate regions of interest in the dorsal and ventral striatum. We also collected a field map (phase-difference B0 estimation; TE1=3.47ms, TE2=5.93ms) to control for spatial distortions, which are particularly problematic in midbrain fMRI (*19, 20*). During acquisition of the anatomical images and the field map (~15min in total) participants lay quietly in the dark.

Subsequently, we collected functional data during six runs of a cue-induced craving task (see below for details). Each functional run consisted of 147 volumes with 58 T2*- weighted echo planar slices (EPIs; TR=2000 ms, TE=30 ms, FoV=210 mm, 70x70 matrix, yielding a voxel size of 3x3x3 mm) acquired as a partial-head volume in an A-P phase encoding direction using interleaved slices. The scanning parameters were extensively piloted (N=11) using the functional localizer task (see below) and the parameters showing the best signal-to-noise ratio (SNR) were selected for the study. Despite the small structure of the SN/VTA, we thus chose 3mm isotropic voxels because of their higher SNR compared to smaller voxels(*62*). The angle of the slices was approximately 20 degrees away from the plane of the standard anterior commissure-posterior commissure (AC-PC) to avoid placing SN/VTA and the sphenoid sinus in the same slice plane. This reduced geometric distortion to the point that standard distortion correction methods could be applied(*19*). The cue induced craving paradigm took approximately 26 minutes total.

Cue induced craving (CIC) task. We designed a novel CIC task to simultaneously measure craving for food and for social interaction, relative to a control. Participants viewed colored images depicting: i) groups of individuals as they meet, talk, laugh, smile, etc.; ii) different kinds of highly palatable foods such as cake, pizza, chocolate, etc., iii) attractive flowers as the control condition.

On each trial, participants saw a single photograph and 3-5 word verbal description, for 5 sec. The combination of visual and verbal cues was intended to maximize deep semantic processing of the relevant attributes. Each trial was followed by a 1s rest period (during which a fixation cross was displayed). Three consecutive trials were presented in a block of the same condition (food, social, control). Each block was followed by a jittered 2-6 second rest period. Subsequently, participants self-reported how much they were currently craving food (on food blocks) or social interaction (on social blocks). After control blocks, participants rated how much they liked the flower image, in order to match the demand for response preparation. A second jittered 2-6 rest period preceded the onset of the next block. In total, participants saw 18 blocks (54 trials) per condition, per scan session. The trials

on each day were unique, so in total participants saw 36 blocks (108 unique images with descriptions) per condition. The duration of the task was approximately 30 minutes – divided into 6 runs, each run had a duration of approximately 5 minutes.

The stimuli for the CIC task were tailored to each individual's preferred foods and modes of social interaction. During the initial screening, participants were asked to list their top ten favorite foods and social activities. Stock photographs illustrating these specific foods and activities were selected from a large public database (https://www.pexels.com/), and then verbal labels were added using the participant's own descriptions. Food descriptions included "fluffy syrup-drenched pancakes", "creamy cheesy macaroni", "refreshing mixed fruit salad", and "yummy vanilla cake with sprinkles". Social descriptions included "chatting and laughing together", "joking around with friends", "supporting each other through workouts", "enjoying a conversation together." Social pictures were all matched for gender of participants (i.e., for a male participant, all social photographs included at least one man). The stimuli were images of strangers, rather than images of the participant's own friends and family, in order to (i) match the food and control images for novelty, since SN/VTA activity is sensitive to novelty(*63*), (ii) match image quality across conditions and participants, and (iii) avoid unmeasured variability in the quality or current status of participants' relationships with specific individuals. Control trials presented attractive photographs of flowers accompanied by positive valence verbal descriptions (Figure 1).

Functional localizer task. During the baseline session, each participant completed a functional localizer at the end of their scan. We anticipated that anatomical localization of SN/VTA might be difficult, given the strong susceptibility to magnetic distortions in the midbrain(*19, 20*). We therefore designed a task to functionally identify relevant midbrain regions in each participant individually. The task was an adapted version of Krebs et al. 2011(*63*). Because midbrain dopaminergic neurons in SN/VTA respond to both novelty and reward(*63-65*), we contrasted novel and rewarding stimuli against familiar and non-rewarding stimuli. However, our pre-registered hypotheses focus on the anatomical localization strategy, so we treat analyses of the functionally localized regions as exploratory.

Before beginning the localizer task, participants memorized a set of 5 images depicting abstract art (all images taken from the free stock pictures site (https://www.pexels.com/)). During the task, the abstract art images served as cues to the condition of the current trial. The task had two conditions: a

reward/loss condition (*reward*) in which participants could earn or lose money depending on whether their responses were correct and fast enough, and a non-reward condition (*non-reward*) in which participants always received $0 regardless of their response. Each trial started with an abstract art image. The previously memorized (*familiar*) images indicated a *non-reward* trial. Abstract art images that were not previously observed (*novel*) indicated a *reward* trial. After the cue, participants saw a number between 1-9 (excluding 5) for 100ms on the screen. Their task was to press an assigned button indicating whether the number is below or above 5 as fast as possible. Initially, correct responses were required in less than 500ms; after 10 consecutive correct answers, this window was reduced to 400ms. After they pressed the button, participants saw the outcome indicating whether they won $1 (*reward* trial, correct response, fast enough), lost $0.20 (*reward* trial, wrong response or too slow), or received $0 (*non-reward* trial). In total, participants played 80 trials (40 trials per condition) and the duration of the task was approx. 10 minutes. Participants responded correctly and within the time limit on 87% of *reward* trials and 69% of *non-reward* trials. The earnings from this task were added to participants' compensation after the baseline session. This design allowed us to compare responses to novel stimuli predicting reward versus familiar stimuli predicting no possibility of reward.

Behavioral data analysis

Questionnaire data. For each participant we collected two measures of social network size (i.e., number of monthly interactions and number of close relationships). These scores indicate the size of participant's social network on different hierarchical levels(*58*). However, because the measures were highly correlated ($r(39)=0.58$, $p<0.001$), we z-transformed and averaged the two measures for each participant. This gave us an indicator of participant's social network size relative to the sample's average social network size. In addition, we calculated a loneliness score for each participant using the UCLA loneliness scale(*57*). We tested how self-report ratings of hunger, food craving, discomfort, happiness and dislike of fasting provided during food fasting changed over the course of 10 hours using paired t-tests comparing the first rating (collected at beginning of fasting) and last rating (collected after 10 hours of fasting). We used the same analysis for the ratings provided during social isolation: loneliness, social craving, discomfort, happiness and dislike of isolation.

<u>fMRI Data analysis</u>

Preprocessing. We used open source preprocessing pipelines for fMRI data, developed through the nipy and nipype(*66*) initiatives. We used the heudiconv python application which uses dcm2niix to convert raw scanner data into the NIFTI image file format, then organizes that data into a BIDS-

formatted directory structure. The FMRIPrep application(*67*) was used to minimally preprocess the anatomical and functional data (using default settings but including susceptibility distortion correction using fieldmaps (see below)). Using FMRIPrep, we skull-stripped anatomical images first roughly using the atlas-based ANTS program(*68*), and then refined it using information from Freesurfer surfaces after reconstruction was completed(*69*). Brain tissue segmentation was performed with the FMRIB Software Library (FSL) FAST program(*70*). Images were spatially normalized to 2mm isotropic MNI-space using the multiscale, mutual-information based, nonlinear registration scheme implemented in ANTS. We visually inspected brain masks, tissue segmentation and freesurfer surfaces. Susceptibility distortion correction was performed using phase-difference B0 estimation(*71*).

A reference image for each run was generated from the input BOLD timeseries. A functional brain mask was created using a combination of FSL, ANTS, AFNI and nilearn tools(*72*). Using FSL's MCFLIRT program(*73*), we estimated and corrected for head motion, resulting in a coregistered BOLD series as well as motion-based confound regressors. Any run containing a framewise displacement greater than 0.4 mm on more than 25% of the total frames was excluded from additional analyses. Additional confound regressors were generated, including other measures of motion (framewise displacement and DVARS and anatomical CompCor(*74*) timeseries derived from CSF and white matter tissue segments). The reference image of each run was aligned with the anatomical image using FreeSurfer's program "bbregister"(*75*). The timepoint-to-functional reference transformation, the functional reference to anatomical transformation, and the anatomical-to-MNI transformation was concatenated into a single transformation and used to transform each functional timeseries into MNI template space. Spatial smoothing was performed on the FMRIPrep outputs with a 6mm smoothing kernel using FSL's SUSAN tool(*76*), which uses segmentation boundaries to avoid smoothing across tissue types. MRIQC, an opensource quality assurance software tool(*77*), was used to generate additional reports which display Image Quality Metrics (IQMs).

Modeling. Analyses were conducted using the nipype framework(*66*). For run-level analyses, the preprocessed timeseries was assessed with algorithms from the Artifact Removal Toolbox (ART)(*78*) to identify frames within the run that have an abnormal amount of motion (0.4 mm of total displacement, or an intensity spike greater than 3 standard deviations from mean). The design matrix included boxcars for the experimental conditions convolved with a double-gamma hemodynamic response function (HRF), and nuisance regressors representing frame-wise motion, the anatomical CompCor regressors derived from white matter and CSF, as well as impulse regressors for volumes

identified by ART. A high-pass filter (120 Hz) was applied to the design matrix and the smoothed data. The model was evaluated using FSL's FILM program(*79*). Subject-level contrast maps were generated using FSL's FLAME(*79*) in mixed-effects mode.

ROI definition. We included functional voxels which overlapped at least 75% with the substantia nigra pars compacta (SN) and the ventral tegmental area (VTA) region from a probabilistic atlas of human subcortical nuclei(*48*). Because the striatum is a major target of projections from midbrain neurons and their firing results in increased DA transmission in the striatum(*18, 50, 51*), we expected to see the same pattern of results in the striatum, i.e.: increased activation to food cues after food deprivation and to social cues after social isolation and a positive correlation between activity in striatum and self-reported craving (for both, food and social craving). Thus, we also included 3 additional ROIs in our analysis: putamen (Pu), Caudate Nucleus (Ca) and Nucleus Accumbens (NAcc) also using the probabilistic subcortical atlas(*48*).

Functional ROI definition. To define subject-specific ROIs, we used individual activations of each participant in the localizer task. The fMRI time series were analyzed using an event-related design approach implemented in the context of the GLM. The model contained two regressors separately modeling the presentation of novel/reward cues, and familiar/non-reward cues (i.e., when the abstract art images were presented, 2s). We also included one regressor for the time period of button press and outcome (1.1s). Because we did not add any jitter between button press and presentation of outcome (as this was not the contrast of interest), we modeled the whole segment as one block. For each participant, we calculated the target contrast *novel reward>familiar non-reward*. We then used a mask encompassing the whole midbrain as the search space for the selection of individual voxels. In each participant we selected the top 100 active voxels within the search space in response to the target contrast.

Univariate Analyses. For our planned analyses, we used mixed effects regressions (using Matlab 2019b's *fitlme* function) to estimate the fixed effects of cue, deprivation session, and the critical interaction of cue and deprivation session, on response magnitude in the ROIs, controlling for each session's average framewise displacement (i.e. head motion), with subject included as a random effect (for further details of the models, see Supplementary Materials). We modeled these effects in the anatomically defined SN/VTA (pre-registered analysis) and in the functionally defined ROI of voxels maximally sensitive to reward and novelty (exploratory analysis).

To test whether these responses were correlated with individual differences in self-reported craving, we calculated the average contrast value (food>flowers and social>flowers) in the anatomically defined SN/VTA for each participant. We used two different approaches to measure participants' self-reported craving. First, we calculated the mean craving rating participants reported on each trial during the CIC task in the scanner (*Craving_CIC*). This measure was exactly comparable across sessions, and simultaneous with the fMRI data acquisition. Second, we took the craving reported by participants on the final online questionnaire, completed after 10 hours of fasting or isolation (*Craving_Q*). On this measure participant only reported craving for the deprived need (food when fasting, social contact when isolated), but this measure provides the most direct measure of the effect of deprivation because it can be compared to the self-report at the beginning of each session. In addition, the *Craving_Q* ratings were completed on a finer scale (0-100 instead of 0-10) and participants had no time restriction when filling out the questionnaires (while during the task, participants had 5s to complete the scales). For these reasons, we include both types of craving ratings and report results as significant at $\alpha<0.025$. We measured correlations between self-reported craving and neural responses for each deprivation session. Because we specifically predicted a positive correlation between craving for the deprived target and response magnitude in SN/VTA, these correlations were tested one-tailed. Data for the analyses was extracted using FSL's *fslmeants* utility and subsequent univariate and correlation analyses were conducted in Matlab 2019b and SPSS 25.

Multivariate Analyses. We next used multivoxel pattern analysis (MVPA) to determine whether the multivariate spatial pattern of activity in SN/VTA is shared for food and social craving. First, we assessed whether we were able to discriminate fMRI patterns between food and control cues in the fasting session in the SN/VTA. For each participant, we partitioned the data into six independent folds (6 runs), and iteratively trained a linear support vector machine (SVM) classifier on 5 runs (i.e. 15 beta estimates per condition) and tested on the left-out run (3 beta estimates per condition). We then averaged the classification accuracy across runs to yield a single estimate for each participant. This within-session classification tested whether we would be able to decode stimulus from multivariate patterns within the SN/VTA.

As a next step, we trained a linear SVM classifier using all 6 runs of the food fasting session on patterns of response to food and flower cues and tested the generalization of the classifier to neural activity measured in response to social and flower cues in the isolation session. We also tested the

generalization of this classifier to neural patterns in response to food cues and control cues in the isolation session to test the generalization of responses to the same stimuli across sessions. In order to be able to compare results between generalizations to the isolation session and the baseline session, we tested the same classifier on social vs control cues and food vs control cues in the baseline session. Thus, we calculated four t-tests testing whether the classifier showed above chance (one-sample t-test across subjects, alpha=(0.05/4)=0.0125) decoding: for(i) isolation session: social cues>control and food cues>control and for(ii) baseline session: social cues>control and food cues>control. If social craving and food craving share a neural basis, we predicted that a classifier trained on food_craved cues will successfully (above chance) classify social_craved cues but will not be able to classify social_noncraved cues. Finally, we used representational similarity analysis to test which pattern of activity is more similar to 'food_craved': social_craved or food_noncraved. We predicted that the presence of a craved object should be more important for SN/VTA activity than the specific object, so we predicted that the pattern of food_craved responses will be *more similar* to the pattern of activity for social_craved than for food_noncraved. Multivariate analyses were conducted with the PyMVPA toolbox in Python (http://www.pymvpa.org) and Matlab2019b.

Correlations univariate fMRI measures and behavioral data. In follow-up analyses, we tested whether individual differences in social network size or chronic loneliness predict the magnitude of self-reported and neural measures of social craving. In addition, we used the UCLA loneliness score obtained from each participant as an indicator of their chronic loneliness. We correlated these two measures with mean values extracted from the midbrain and striatum ROIs from the contrast social_craved>control.

Results

Description of study sample.

The forty participants were within a healthy weight range (BMI mean (standard deviation)=22.8(2.2)), reported frequent social interactions (monthly interactions, mean=49.1(31.7); minimum=10) and close relationships (number of close relationships, mean=12.3(5.1); minimum=3). Participants reported relatively(*57*) low levels of pre-existing loneliness (UCLA loneliness scale, mean=33.2(6.3), maximum=47 out of 80).

Subjective social craving can be evoked by acute objective social isolation

After ten hours of social isolation, participants reported substantially increased social craving ($t(39)=5.35$, $p<0.001$), loneliness ($t(39)=5.17$, $p<0.001$), discomfort ($t(39)=5.57$, $p<0.001$) and dislike of isolation $t(39)=4.13$, $p<0.001$), and decreased happiness ($t(39)=-4.21$, $p<0.001$). Thirty-six out of forty individual participants reported feeling more lonely after isolation. As expected, after ten hours of food fasting participants reported increased food craving ($t(36)=17.40$, $p<0.001$), hunger ($t(36)=23.90$, $p<0.001$), discomfort ($t(36)=11.74$, $p<0.001$) and dislike of fasting ($t(36)=5.70$, $p<0.001$), and decreased happiness ($t(36)=-3.25$, $p=0.002$). Thus, both forms of abstinence evoked craving for the specifically deprived need, along with general discomfort and decreased happiness. Though we note that social craving after isolation was more variable, across participants, than food craving after fasting (mean(standard deviation) of craving ratings on questionnaire, after 10 hours: food craving=80.25(19.39); social craving=66.38(24.52), Figure 2; Levene's test indicated unequal variances ($F(76)=15.86$, $p<0.001$).

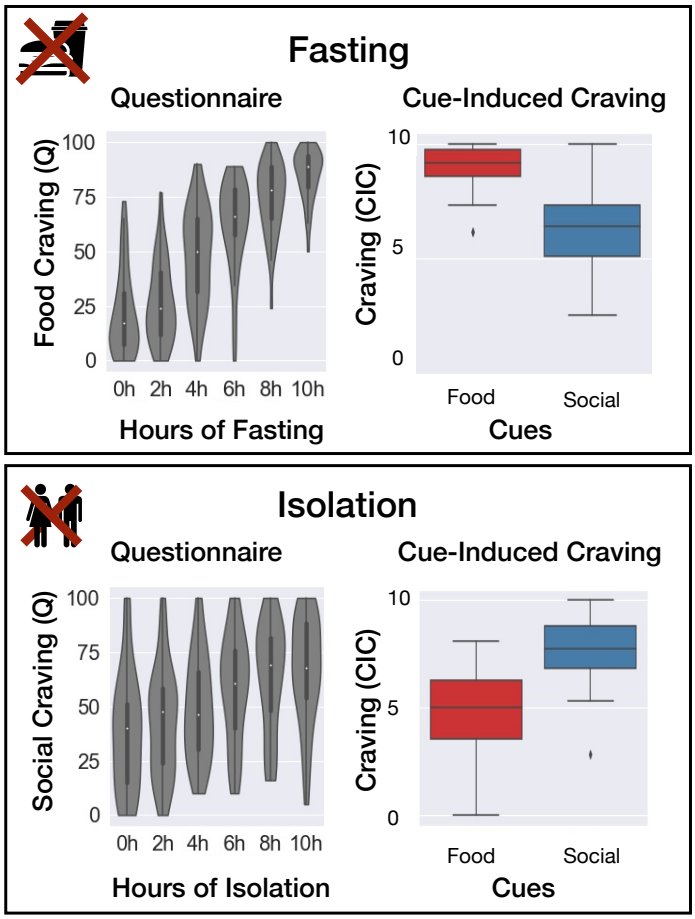

Figure 2. Behavioural results: The upper panel shows changes in self-reported food craving over time during fasting (left) and in comparison to ratings of social craving during the cue induced craving task (right). The lower panel shows changes

in self-reported social craving over time during isolation (left) and in comparison to ratings of food craving during the cue induced craving task (right).

Following isolation, social cues evoke neural signatures of craving

Our primary hypotheses concerned activity in the dopaminergic midbrain in response to food cues and social cues, after fasting versus isolation. In the anatomically defined SN/VTA (Figure 3A), responses to food cues were higher after fasting than after isolation (b=0.06, t=3.1, 95% CI=[0.0.02,.09], p=0.002), but responses to social cues were not higher, on average, after isolation than after fasting (b=-0.03, t=-1.3, 95% CI=[-0.6,0.01], p=0.18; for full results of the model including all main effects, see Supplementary Materials). In the midbrain functional ROI (voxels maximally sensitive to reward and novelty, Figure 3B), responses to food cues were higher after fasting than after isolation (b=0.03, t=3.3, 95% CI=[0.01,0.05], p=.001), and responses to social cues were higher after isolation than after fasting (b=0.03, t=2.5, 95% CI=[0.006, 0.05], p=0.01).

SN/VTA responses to both food and social cues were correlated with self-reported craving. After fasting, in the anatomical SN/VTA, response to food cues (versus flowers) was positively correlated with the participant's self-reported food craving measured during the cue-induced craving task (*Food_Craving_CIC*: r(38)=0.31; p=0.023, Figure 3C), but not with self-reported food craving on the final questionnaire (*Food_Craving_Q,* r(36)=0.06; p=0.352). After isolation, SN/VTA response to social cues (versus flowers) was positively correlated with self-reported social craving on the final questionnaire (*Social_Craving_Q*, r(38)=0.32; p=0.023; Figure 3 C); though SN/VTA activity was not correlated with social craving measured during the cue-induced craving task (*Social_Craving_CIC*: r(38)=0.07; p=0.34).

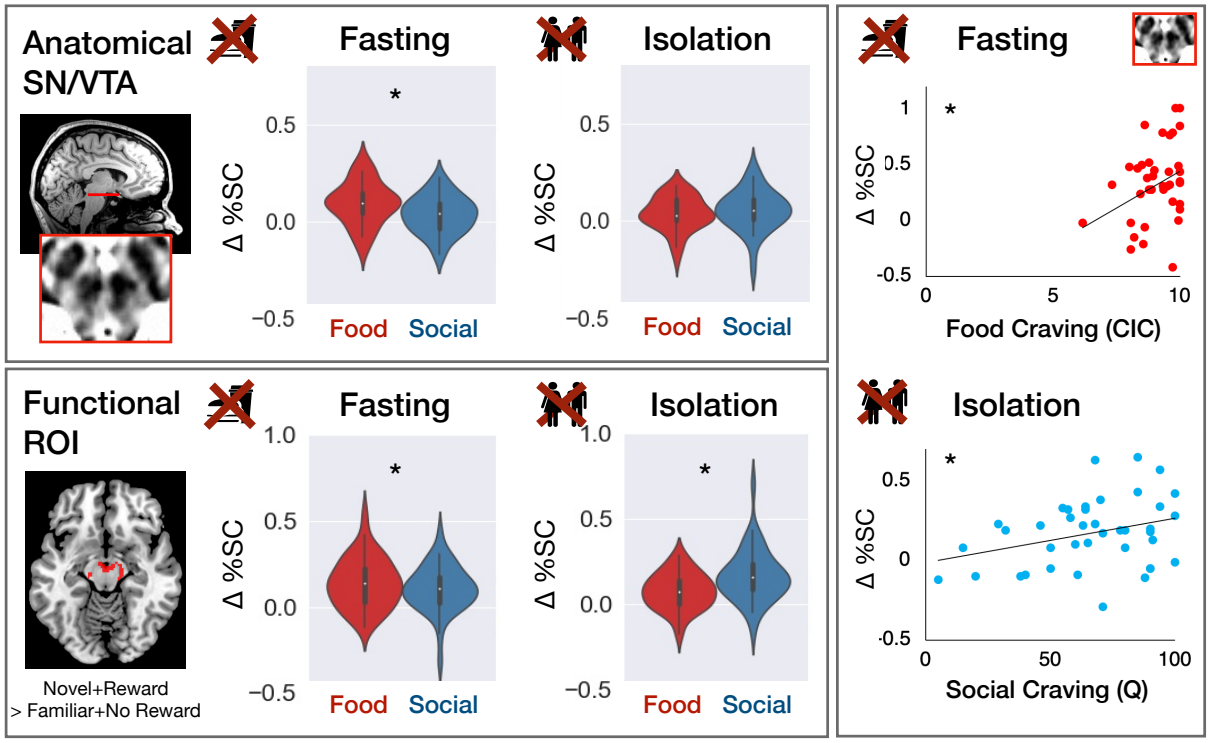

Figure 3. Effects of food fasting on univariate activity within the anatomical ROI (upper left panel), the functional ROI (lower left panel) and correlations with self-reported craving (right panel). The violin plots depict the difference (in percent signal change) in response to food cues (contrast: food>flowers) and social cues (contrast: social>flowers) after fasting and after isolation. The violins illustrate the distribution of the data, the white dots indicate the median, the bold dark grey vertical line the interquartile range and the thin grey lines the upper/lower adjacent values. Left upper panel: Responses in the anatomical SN/VTA were higher for food after fasting. Left lower panel: Responses in the midbrain functional ROI were higher for food after fasting and for social cues after isolation. Right panel: In the anatomical SN/VTA, responses to food cues were correlated with craving reported in the Cue Induced Craving task, following fasting (upper panel) and responses to social cues were correlated with craving reported on the final Questionnaire, following isolation (lower panel).

As a direct test of the similarity of activity patterns for food cues after fasting, and social cues after isolation, we trained a classifier on the pattern of activity in the SN/VTA after fasting to food cues and flower images. This learned classifier then generalized to above chance decoding of food from flower images on both of the other sessions (Isolation session: mean accuracy=0.54; $t(39)=3.01$, $p=0.005$; Baseline session: mean accuracy=0.55; $t(39)=3.35$, $p=0.002$). The same learned classifier could also decode social cues from flower images after isolation (mean accuracy=0.54; $t(39)=3.53$, $p=0.001$). On the baseline day, the classification accuracy did not survive correction for multiple comparisons ($\alpha = 0.05/4$; mean accuracy=0.53; $t(39)=2.59$, $p=0.013$). The pattern of SN/VTA activity in response to social cues on the isolation day was more similar to the pattern of food cues on the

fasting day, than to food cues on the baseline day (mean correlation: social_craved-food_craved=0.34, social_craved-food_noncraved=0.20; t(39)=2.02, p=0.025). Indeed, SN/VTA responses to different stimuli in a similar motivational state (social_craved-food_craved=0.34) trended towards being more similar to each other than the responses to the same stimuli across different motivational states (food_craved–food_noncraved; mean correlation: 0.25; t(39)=1.4, p=0.08).

In sum, these results suggest that across all participants, SN/VTA shows an increased response to social cues after objective social isolation, in a pattern that is similar to the response to food cues when hungry; the magnitude of this response was variable across participants, and larger in those who reported more social craving after the acute isolation period. We predicted that individual variability in response to objective isolation might reflect pre-existing differences in participants' social network size and/or chronic loneliness. Consistent with this prediction, participants with higher levels of chronic loneliness during the initial screening reported less craving for social contact after 10 hours of isolation in response to the social cues in the cue-induced craving task (*Social_Craving_CIC*: r(38)=-0.36; p=0.020; two-tailed) and somewhat less craving on the online questionnaire (*Social_Craving_Q*: r(38)=-0.30; p=0.059; two-tailed). People with higher pre-existing chronic loneliness also showed a muted response in SN/VTA to social cues after acute isolation (r(38)=-0.35; p=0.027; two-tailed). Individual differences in social network size did not predict either self-reported or neural responses to acute social isolation (all p-values >= 0.18). We explored whether pre-existing loneliness was also associated with different responses to food cues after fasting and find that while loneliness did not affect self-reported food craving (p-values p>0.307), higher loneliness was associated with lower post-fasting SN/VTA responses to food cues (r(38)=-0.32; p=0.042; two-tailed).

Comparison to the baseline session

In addition to directly comparing responses after fasting and isolation, we conducted exploratory analyses comparing responses after fasting, and after isolation, to the baseline day with no deprivation. Self-reported craving for food and social contact were higher on the relevant deprived day than on the baseline day (*Food_Craving_CIC*): (t(39)=7.94; p<0.001, two-tailed, *Social_Craving_CIC* (t(39)=4.15; p<0.001, two-tailed). However, on the baseline day, SN/VTA and midbrain responses to both food and social cues were quite variable, and on average as high as on the relevant deprived day. In the anatomical ROI, a mixed effects regression model found no interaction between the baseline and other sessions. In the functional midbrain ROI, relative to the baseline session, responses to food cues were low after isolation (b=-0.06, t=-2.4, 95% CI [-.11, -.01], p=0.02) and responses to social cues were low

after fasting (b=-0.01, t=-1.8, 95% CI [-.11, 0.003], p=0.07); the midbrain ROI response to food cues did not differ between fasting and baseline day (b=0.004, t=0.14, 95% CI [-.05, .06], p=0.88), or to social cues on the isolation and baseline day (b=0.004, t=0.14, 95% CI [-.05, .06], p=0.89). We also find no suprathreshold difference between baseline days and deprived days in a whole brain analysis (see Supplemental Materials).

Individual differences in baseline responses to food and social cues were systematic, though: self-reported food craving (*Food_Craving_CIC*) correlated with SN/VTA responses to food cues (r(38)=0.33; p=0.04; two-tailed) and self-reported social craving (*Social_Craving_CIC*) correlated with SN/VTA responses to social cues (r(38)=0.37; p=0.02; two-tailed). Similar to responses after isolation, on the baseline day, participants higher in chronic loneliness reported less social craving immediately before the scan (r(38)=-0.40; p=0.01; two-tailed), though chronic loneliness did not affect craving ratings during the CIC task (r(38)=-0.15; p=0.37; two-tailed). Participants who reported higher levels of chronic loneliness during the initial screening also showed a muted response in SN/VTA to social cues (r(38)=-0.46; p=0.003; two-tailed) and to food cues (r(38)=-0.38; p=0.016; two-tailed) during the baseline scan.

Responses in striatum

Although our primary hypotheses focused on the dopaminergic midbrain, and particularly SN/VTA, we also investigated responses in the striatum, a major target of projections from SN/VTA. A mixed effects regression model tested effects of cue (food, social, flowers), session (fasting, isolation) and subregion of the striatum (nucleus accumbens (NAcc), caudate nucleus (Ca), and putamen (Pu) (dummy coded)). Food cues (compared to flowers) evoked a stronger response after fasting (compared to after isolation) in nucleus accumbens (NAcc, b=0.04, t=3.1, 95% CI [.02,.07], p=0.002) but not in caudate nucleus (Ca, b=0.007, t=0.98, 95% CI [-.01,.02], p=0.32). Social cues evoked a stronger response after isolation (compared to after fasting) in Ca (b=0.02, t=1.98, 95% CI [.00,.04], p=0.047) but not in NAcc (b=0.02, t=1.2, 95% CI [-.01,.05], p=0.21). An exploratory whole brain random effects analysis yielded converging results: spatially non-overlapping activity for food craving (in nucleus accumbens, periaquductal gray, amygdala, among others) and for social craving (in caudate nucleus, dorsomedial prefrontal cortex, among others; see Supplementary Materials). Thus, while the responses in SN/VTA were similar and overlapping for food craving and social craving, responses in the striatum and the rest of the brain were dissociable. We conducted exploratory analyses to test whether subjective craving of food and social contact (*Craving_CIC*) was correlated with striatal activity

for any condition or any of the three subregions (reporting results significant at $\alpha<0.017$ to correct for multiple comparisons) and found no significant correlation in the striatum ROIs (all p-values>0.043).

Discussion

In humans, acute mandatory social isolation evokes a neural "craving" response to social cues. Midbrain regions showed selective responses to food cues after fasting and to social cues after isolation. SN/VTA activity was higher in people who self-reported wanting food or social interaction more, following deprivation. The multivariate pattern of SN/VTA response was similar for food and social interaction when craved. People who are forced to be isolated crave social interactions similarly to the way a hungry person craves food.

Our findings are consistent with results from the mouse model showing that dopaminergic neurons in the midbrain represent the neural substrate of social isolation(*44*). In mice, dopaminergic neurons in the midbrain appear to encode an aversive "loneliness-like" state that motivates social engagement. Our findings suggest that there is a similar mechanism underlying social craving in humans.

The first challenge for this research was to induce a subjective state of social craving using an experimentally induced period of objective isolation. Despite the fact that isolation lasted only ten hours, and the participants knew exactly when it would end, participants reported more loneliness and social craving at the end of the day than they did at the beginning. For our participants, who are all highly socially connected, a day of social isolation was a very large deviation from typical rates of social interaction. Although being alone is not inherently aversive for people (i.e., when chosen intentionally, solitude can be restful and rejuvenating(*80, 81*)), our isolation paradigm was subjectively aversive: participants felt more uncomfortable and less happy at the end of the day. In the current paradigm, isolation was likely made more salient by the externally mandated (not personally chosen) restrictions on participants' behaviour, including bans on email, social media, fiction, films, music, and other forms of virtual and fictional connectedness(*82*) (though participants did have access to games, puzzles, and reading material). The cessation of virtual social interaction was a substantial change: typical young adults currently use social media for social interactions more than two hours per day(*83*). In all, this experiment demonstrates that acute objective social isolation can induce subjective social craving in human participants. This paradigm could be useful for future research investigating, for example, how

objective isolation is experienced by different human groups (e.g., adolescents, older adults) and how this experience is modulated by social media usage.

Loneliness and social craving were more variable across participants than hunger and food craving after 10 hours of fasting. Variability in the effect of social isolation was partly explained by pre-existing variability in participants' chronic loneliness: participants who were more lonely prior to the experiment showed attenuated social motivation after isolation and even at baseline (even though no participants were severely lonely or isolated). This pattern is consistent with prior evidence that chronic loneliness is associated with reduced social approach motivation(*84*): loneliness is associated with higher self-centeredness(*85*), preference for larger interpersonal space(*86*), and decreased motivation to approach good social outcomes(*87*). In future studies, it could be interesting to investigate the interactive effects of chronic and acute isolation on social motivation.

The second challenge for this research was to measure fMRI activity in SN/VTA, a small structure in the midbrain that is prone to substantial distortion. We used an optimized imaging protocol(*19*) and a newly available midbrain atlas(*48*), and validated our approach by measuring previously established SN/VTA responses to (i) reward-predicting and novel stimuli(*20, 63, 64*) in the functional localizer task, and (ii) food cues following fasting(*28, 88, 89*). To measure craving-related activity, we designed a cue-induced craving paradigm – a classic paradigm used to measure craving responses in the brain(*90-94*). Food cues were images of each participant's favourite foods (as reported on the screening survey), accompanied by brief verbal descriptions to promote recognition of the relevant attributes of the image and deeper semantic encoding. Similarly, social cues were images of people engaged in each participant's favourite social activities. We chose to use images of strangers, rather than images of the participant's own friends and family, so that all images in all conditions would be novel to participants, since SN/VTA activity is sensitive to novelty(*63*). Still, it is possible that images of specific loved ones would evoke an even stronger social craving response than the one reported here.

Using this modified cue-induced craving task, we found that after deprivation, SN/VTA responses were enhanced selectively for cues to the deprived need (compared to cues to the non-deprived target). That is, although participants reported general discomfort and reduced happiness after both fasting and isolation, SN/VTA responses were selective to food after fasting and to social cues after isolation. These results fit with the intuitive prediction that the deprivation of a need causes increased craving for the specific need(*95*). By contrast, though, in animal models social isolation does sometimes cause

increased food consumption(*96, for review*) and other general changes in motivational systems(*14, for review*). In rodents, for example, social isolation increases voluntary alcohol intake(*42, 97, 98*) as well as morphine consumption(*99, 100*), and can alter DA release in response to alcohol intake(*97*). A key predictor may be the duration (and possibly the developmental timing) of the isolation: short term acute isolation in adults may cause selective social motivation, whereas long-term or developmental isolation could lead to more general compensatory changes. Indeed, in our sample we find that participants who report higher levels of chronic loneliness show reduced activity in the SN/VTA in response to social cues, consistent with prior evidence(*101*) (but see(*102*), (*103*)), but also to food cues, including on the baseline day. Thus, chronic loneliness might lead to broad alterations in the human motivation system, as in the animal models. However, the causal mechanism underlying these correlations remains unclear: individuals with reduced activity in motivational brain areas might be more prone to becoming lonely. This possibility highlights the importance of experimentally inducing acute isolation, to disentangle direct effects of isolation per se from individual differences in reward seeking behavior more generally.

In the midbrain, responses to food when hungry and social cues when isolated appear to rely on similar neural populations. Patterns of response in SN/VTA in response to food when hungry were more similar to the pattern of response to social cues when isolated than to responses to food when sated. Unexpectedly, though, we found distinct responses in the striatum, the major target of dopaminergic projections from SN/VTA. Fasting enhanced responses to food cues mostly in nucleus accumbens, whereas isolation enhanced response to social cues mostly in the caudate nucleus. Previous studies find the most consistent effects of food craving in the nucleus accumbens, though some studied do report responses to craved food in caudate nucleus(*29, 104, for reviews*). Activity in the caudate nucleus has previously been correlated with subjective ratings of craving across different targets of desire (such as drugs and food)(*105-107*), though we observed no correlation between caudate activity and self-reported craving in the current study.

Caudate nucleus activity for social craving is consistent with evidence of caudate activity when people re-live experiences of rejection by a significant other (*108, for meta-analysis*). Social rejection may thus evoke a craving response similar to effects of social isolation. However, we suggest that social rejection (being deliberately and specifically excluded from social interaction) is conceptually distinct from social isolation (being unable to access social interaction). By contrast to the under-studied effects of social isolation, there is extensive research on the behavioural and neural sequelae of social rejection(*108,*

109, for reviews). Unexpected and undeserved deliberate rejection or exclusion is painful, and evokes a pattern of neural response associated with processing of aversive states like physical pain, including bilateral anterior insula and anterior cingulate cortex (ACC) (*108, 109, for reviews*). These brain areas were not recruited by social craving in the current task (see Supplemental material table S2). Rejection and isolation are also likely to have different emotional and behavioural effects. Social rejection can lead to increased motivation to affiliate with others but also to withdrawal and anger(*110, 111*); whereas isolation may be more likely to cause approach and a motivation to re-connect. Thus, while both social isolation and social rejection are aversive to humans, these states are likely distinct both behaviourally and neurally.

Another unexpected pattern emerged on the baseline day, when participants were scanned after following their regular daily routine for both food consumption and social interaction. On the baseline day, SN/VTA responses to both food and social cues were, on average, as high as on the relevant deprived day even though on average participants self-reported higher craving on the deprived days. On baseline days, the magnitude of SN/VTA activity was correlated with self-reported craving. Participants who reported feeling more craving for food, or social interaction, on the baseline day showed correspondingly higher SN/VTA response to those cues. Thus, it appears, that even without specific deprivation, SN/VTA shows craving responses for food and social contact which correspond to participants' subjective feelings of craving. Rewarding stimuli (including food and social contact) are craved even without specific deprivation(*16*). Possibly our participants' daily routines do not satisfy their needs for food and social contact. In addition, at baseline, participants' motivation may be spread generally across multiple sources of reward; specific acute deprivation might serve to narrow (rather than enhance) the brain's motivational responses to the deprived target. If so, acute hunger might reduce social motivation compared to baseline. Indeed, there is some evidence that people are less prosocial when hungry(*112*), consistent with a reduction in social motivation caused by acute hunger, although see(*113*).

The more selective SN/VTA response to social cues after isolation, as well as to food cues after fasting, fits the intuitive idea that positive social interactions are a basic human need, and acute loneliness is an aversive state that motivates people to repair what is lacking, similar to hunger. Thus, our research provides empirical support in human participants for the "social homeostasis" hypothesis developed based on animal models(*46*). Despite differences in the duration and setting of social isolation, and in the anatomy of DA midbrain structures, both humans and mice seem to show midbrain craving

responses for social interaction, as well as for food. Even this broad similarity of neural responses in mice and humans is encouraging for the translational prospects of mouse models of mental health disorders that affect social motivation – for example autism spectrum disorder(*114, 115*), social anxiety disorder(*116*), or depression(*117*).

A vital question for future research is how much, and what kinds of positive social interaction are sufficient to fulfill this basic need and thus eliminate the neural craving response. Technological advances offer incessant opportunities to be virtually connected with others, despite physical separations. Yet, some have argued that using social medial only exacerbates subjective feelings of isolation(*118, for review*) but see(*119, 120*). Future studies could compare SN/VTA responses to social cues following isolation with and without access to social media. The capacity for virtual interactions to fulfill social needs is particularly relevant when large populations are required to self-isolate, for example during a global pandemic. In early 2020, millions of humans experienced a sudden externally mandated period of relative or complete physical isolation from others, as public health officials sought to slow the spread of an infectious novel corona virus. This unprecedented upheaval in people's social routines emphasized the need for a better understanding of human social needs and the neural mechanisms underlying social motivation. The current study provides a first step in that direction.

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