Reduced anhedonia following internet-based cognitive-behavioral therapy for depression is mediated by enhanced reward circuit activation

Shir Hanuka[1,*], Elizabeth A. Olson[2,3,*], Roee Admon[1,4] (iD), Christian A. Webb[2,3], William D. S. Killgore[5], Scott L. Rauch[2,3], Isabelle M. Rosso[2,3,†] and Diego A. Pizzagalli[2,3,†]

[1]School of Psychological Sciences, University of Haifa, Haifa, Israel; [2]Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA, USA; [3]Department of Psychiatry, Harvard Medical School, Boston, MA, USA; [4]The Integrated Brain and Behavior Research Center (IBBRC), University of Haifa, Haifa, Israel and [5]Department of Psychiatry, University of Arizona, Tucson, AZ, USA

Abstract

Background. Major depressive disorder (MDD) is a highly prevalent psychiatric condition, yet many patients do not receive adequate treatment. Novel and highly scalable interventions such as internet-based cognitive-behavioral-therapy (iCBT) may help to address this treatment gap. Anhedonia, a hallmark symptom of MDD that refers to diminished interest and ability to experience pleasure, has been associated with reduced reactivity in a neural reward circuit that includes medial prefrontal and striatal brain regions. Whether iCBT can reduce anhedonia severity in MDD patients, and whether these therapeutic effects are accompanied by enhanced reward circuit reactivity has yet to be examined.
Methods. Fifty-two MDD patients were randomly assigned to either 10-week iCBT (*n* = 26) or monitored attention control (MAC, *n* = 26) programs. All patients completed pre- and post-treatment assessments of anhedonia (Snaith–Hamilton Pleasure Scale; SHAPS) and reward circuit reactivity [monetary incentive delay (MID) task during functional magnetic resonance imaging (fMRI)]. Healthy control participants (*n* = 42) also underwent two fMRI scans while completing the MID task 10 weeks apart.
Results. Both iCBT and MAC groups exhibited a reduction in anhedonia severity post-treatment. Nevertheless, only the iCBT group exhibited enhanced nucleus accumbens (Nacc) and subgenual anterior cingulate cortex (sgACC) activation and functional connectivity from pre- to post-treatment in response to reward feedback. Enhanced Nacc and sgACC activations were associated with reduced anhedonia severity following iCBT treatment, with enhanced Nacc activation also mediating the reduction in anhedonia severity post-treatment.
Conclusions. These findings suggest that increased reward circuit reactivity may contribute to a reduction in anhedonia severity following iCBT treatment for depression.

Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric condition, associated with substantial impairments in daily function and a significant reduction in quality of life (World Health Organization, 2017). As such, MDD is a worldwide leading cause of societal and economic burden, disability, and suicide risk (Ferrari et al., 2013; Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Lopez & Murray, 1998; Moitra et al., 2021). Multiple treatment modalities are available for MDD patients, including antidepressant medications, psychotherapies, and brain stimulation techniques. Although these treatments have proven beneficial to a certain degree, only 30% of patients experience full remission following treatment (Cuijpers et al., 2021; Gaynes et al., 2008; Kaur & Sanches, 2021). Even more troublesome, the majority of depressed individuals does not receive treatment, or does so with a substantial delay, thus limiting potential clinical and functional improvement (Batterham, Calear, Farrer, Gulliver, & Kurz, 2021). It is therefore critical to continue to improve existing therapeutic methods for MDD and develop new approaches that could address treatment gaps (Ormel, Kessler, & Schoevers, 2019). One promising advancement in this direction is to harness one of the most extensive resources of the 21st century, the internet. Internet-based interventions have the potential to aid depressed individuals to overcome many of the barriers associated with traditional face-to-face psychotherapy or pharmacotherapy, including high costs, long waitlists, limited access to treatment, and perceived stigma. Several recent meta-analyses have indeed established the therapeutic efficacy of internet-based interventions in producing both short-term and long-lasting reductions in depression severity (Etzelmueller et al., 2020; Josephine, Josefine, Philipp, David, & Harald, 2017). Among internet-based interventions, internet-based

cognitive-behavioral therapy (iCBT) has been particularly popular over the past decade (Furukawa et al., 2018; Rosso et al., 2017). Studies assessing iCBT efficacy have established it as an efficacious evidence-based therapy for MDD that outperforms treatment as usual in terms of clinical outcomes, and leads to substantial remission rates (Karyotaki et al., 2021).

Recently, it has become apparent that further advancement towards informed clinical care for MDD may stem from focusing on its intermediate phenotypes, as these approaches may account for clinical heterogeneity among MDD patients and enable a more accurate characterization of underlying neural mediators. Anhedonia, a hallmark symptom of MDD that refers to loss of interest in previously enjoyed activities and diminished ability to experience pleasure from such activities, has emerged as one such promising candidate (Admon & Pizzagalli, 2015; Hasler, Drevets, Manji, & Charney, 2004; Pizzagalli, 2014; Webb et al., 2016). Indeed, vast preclinical and clinical evidence has associated anhedonia in MDD with reduced activation and connectivity of a neural network that subserves reward-related processes (i.e. reward circuit) (Cooper, Arulpragasam, & Treadway, 2018; Der-Avakian & Markou, 2012; Haber & Knutson, 2010; Höflich, Michenthaler, Kasper, & Lanzenberger, 2018; Nestler & Carlezon, 2006; Wang, Leri, & Rizvi, 2021). More specifically, a robust existing literature identifies the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), orbital prefrontal cortex (OFC), amygdala, and striatal regions [e.g. caudate, putamen, nucleus accumbens (Nacc)] as key reward circuit structures that are associated with anhedonia in MDD (Der-Avakian & Markou, 2012; Haber & Knutson, 2010; Pizzagalli et al., 2009; Wacker, Dillon, & Pizzagalli, 2009). The subgenual ACC (sgACC) has also emerged as a region of particular interest in the depression literature; as a sub-region of the vmPFC, the sgACC is implicated in reward processing and anhedonia, as well as in treatment response in MDD (Alexander et al., 2019; Azab & Hayden, 2018; Dunlop et al., 2017; Gabbay et al., 2013; Guo, Hyett, Nguyen, Parker, & Breakspear, 2016; Nakamura et al., 2021; Narushima, McCormick, Yamada, Thatcher, & Robinson, 2010; Strait et al., 2016; Wang et al., 2019). Of note, reward circuit dysfunction in MDD has been shown to occur in both anticipatory (loss of interest) and consummatory (diminished ability to experience pleasure) phases (Keren et al., 2018; Nielson et al., 2021; Rizvi, Pizzagalli, Sproule, & Kennedy, 2016; Zhang, Chang, Guo, Zhang, & Wang, 2013).

Critically, there is also evidence to suggest that anhedonia may respond to forms of psychosocial treatment including CBT, but there is significant heterogeneity in the extent to which individuals experience improvement in anhedonia in response to psychotherapy (Boumparis, Karyotaki, Kleiboer, Hofmann, & Cuijpers, 2016), which may relate to responsivity in brain structures involved in reward processing. Indeed, Boumparis and colleagues found that enhanced reactivity within the reward circuit post-treatment mediated treatment-related reductions in anhedonia severity among MDD patients (Boumparis et al., 2016). Similarly, increased Nacc and caudate reactivity in response to reward following antidepressant treatment, as well as increased cortico-striatal connectivity, was associated with a reduction of anhedonic and depressive symptoms post-treatment (Admon et al., 2015b; Heller et al., 2013; Takamura et al., 2017; Yang et al., 2018). Deep brain stimulation (DBS) targeting either the Nacc or the sgACC has also been associated with increased activation in these regions and reduced anhedonic symptoms among treatment-resistant depressed patients

(Conen, Matthews, Patel, Anton-Rodriguez, & Talbot, 2018; Schlaepfer et al., 2008). Cognitive-behavioral therapy (CBT) has been linked to increased sgACC responsivity to positive stimuli, as well as to decreased responsivity to negative stimuli, with the latter associated with a reduction in depressive symptoms (Yoshimura et al., 2014). Changes in sgACC connectivity patterns following CBT were also associated with symptom improvement in depressed adolescents (Straub et al., 2017).

No study to date has assessed whether iCBT may lead to reduced anhedonia severity in MDD, nor whether these putative beneficial effects are associated with, and potentially mediated by, enhanced reward circuit activation and connectivity. To address these critical gaps, we conducted a longitudinal neuroimaging study in a sample of adult depressed individuals before and after a 10-week technician-assisted iCBT intervention that has previously been shown to yield significant reductions in depressive symptoms (Rosso et al., 2017). All participants completed the monetary incentive delay (MID) task during functional magnetic resonance imaging (fMRI) scans before and after the 10-week iCBT program, to enable examination of pre- to post-treatment changes in neural activation and connectivity patterns in response to reward anticipation and reward feedback. Anhedonia severity was assessed pre- and post-treatment using the Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995). Demographically matched groups of depressed individuals undergoing a 10-week monitored attention control (MAC) program, and of healthy controls (HC), also completed two SHAPS assessments and two fMRI scans of the MID task 10 weeks apart. We hypothesized that iCBT would be associated with reduced anhedonia severity in MDD, and that this effect would be mediated by enhanced reward circuit activation and connectivity post-treatment. More specifically, we hypothesized that following iCBT anhedonia severity would be reduced while neural activation and connectivity in response to reward in cortical and striatal brain regions of the reward circuit would be increased. We further hypothesized that enhanced reward circuit reactivity following iCBT would be associated with, and potentially mediate, the reduction in anhedonia severity.

Methods

Participants

Data were derived from a randomized clinical trial of iCBT for adults (18–45 years of age) with a diagnosis of MDD (Rosso et al., 2017). The present sample includes 94 individuals who completed the full experiment protocol, divided into three groups: (1) Individuals meeting DSM-IV criteria for MDD randomized to iCBT ($n = 26$); (2) Individuals meeting DSM-IV criteria for MDD randomized to MAC ($n = 26$); and (3) Healthy controls ($n = 42$) (Table 1). The study was approved by the Institutional Review Board (IRB) of Partners Healthcare (now Mass General Brigham; ClinicalTrials.gov Identifier: NCT01598922), and the US Army Human Research Protections Office (HRPO), and all participants provided written informed consent. Inclusion criteria included a primary diagnosis of current MDD according to the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR; (American Psychiatric Association, 2000)], a Patient Health Questionnaire-9 [PHQ-9; (Kroenke, Spitzer, & Williams, 2001)] score between 10 and 23 (inclusive), age between 18 and 45, ability to read English, regular access to a phone and computer with Internet access, absence of psychotropic

Table 1. Demographic and clinical characteristics of participants

Demographic characteristics	HC ($n = 42$)		MAC ($n = 26$)		iCBT ($n = 26$)	
Female [n (%)]	23	(54.8)	18	(69.2)	16	(61.5)
Race [n (%)]						
White	25	(59.5)	16	(61.5)	16	(61.5)
Black	4	(9.5)	1	(3.8)	1	(3.8)
Asian	9	(21.4)	4	(15.4)	3	(11.5)
More than one race	0	(0)	2	(7.7)	1	(3.8)
Other	3	(7.2)	1	(3.8)	1	(3.8)
Unknown	1	(2.4)	2	(7.7)	4	(15.4)
Age [mean (s.d.)]	28.45	(6.96)	28.73	(6.70)	30.42	(8.30)
Clinical characteristics	HC ($n = 42$)		MAC ($n = 26$)		iCBT ($n = 26$)	
PHQ-9 [mean (s.d.)]						
Pre-treatment	0.60[1,2]	(0.91)	14.19[1,5]	(3.23)	13.77[2,6]	(3.44)
Post-treatment	0.65[3,4]	(1.08)	10.46[3,5,7]	(4.85)	7.3[4,6,7]	(4.97)
SHAPS [mean (s.d.)]						
Pre-treatment	18.21[1,2]	(3.65)	33.11[1,5]	(5.80)	29.76[2,6]	(5.96)
Post-treatment	17.85[3,4]	(3.93)	29.24[3,5]	(5.88)	24.76[4,6]	(4.75)

SHAPS, Snaith Hamilton Pleasure Scale; PHQ-9, Patient Health Questionnaire; s.d., standard deviation.
Values represent n (percentages in parentheses) or means (s.d.s in parentheses). Groups with matching superscripts were significantly different when compared using independent t tests, paired t tests, or χ^2 analyses ($p < 0.05$).

medications for at least 2 weeks (6 weeks for fluoxetine, 6 months for neuroleptics) and right-handedness. Exclusion criteria included severe depression (initial PHQ-9 total score > 23), significant suicidal ideation (initial PHQ-9 item 9 score > 1), lifetime history of bipolar disorder or schizophrenia spectrum disorder, current or past alcohol or substance dependence, current alcohol abuse, current or past substance abuse, use of recreational drugs except cannabis within the past year, use of cannabis within the past month, current participation in any form of cognitive-behavioral therapy, history of electroconvulsive therapy, less than ninth-grade education and MRI contraindication.

Procedure

Study procedures have been previously described (Rosso et al., 2017; Webb et al., 2018). In brief, following an initial telephone screening procedure, participants were invited for a laboratory visit to determine eligibility based on the Structured Clinical Interview for DSM-IV (SCID), PHQ-9 and MRI safety screening. Participants who met the selection criteria were invited for a second laboratory visit during which they completed a battery of self-report questionnaires including the SHAPS (Snaith et al., 1995), and underwent an fMRI scan while completing the MID task (Knutson, Westdorp, Kaiser, & Hommer, 2000). At the end of this visit, MDD participants were notified of their treatment group assignment (iCBT or MAC). Participants in the MAC group were informed that they would receive access to the iCBT program after completing the 10-week monitoring period and the third laboratory visit. Following the 10-week treatment (or MAC) period, participants returned for a third laboratory visit that included a repeat of the SHAPS questionnaire and the fMRI MID scan. HC participants underwent a similar protocol without any intervention between the two fMRI scans.

Participants were remunerated up to $500 based on the time invested in completing the study.

Internet-based cognitive-behavioral therapy (iCBT) treatment program

This study used a modified version of the Sadness Program, a technician-assisted iCBT treatment program that was originally developed at the University of New South Wales (UNSW) (Perini, Titov, & Andrews, 2009; Titov et al., 2010). Modifications involved language adaptations and minor content alterations for relevance to American culture. Participants logged into the system six times during the 10-week intervention period. Participants in the iCBT group then had access to the weekly CBT lessons, completed sequentially from lesson one to six. Lessons were presented as an illustrated cartoon strip about a character named 'Jess' who experiences depression and anxiety symptoms, and who learns how to alleviate these symptoms using CBT. After completing each lesson, iCBT participants could download a lesson summary, homework assignments, and optional supplemental resources. Participants in the MAC group also logged into the online system six times during the 10-week period, but their 'lessons' consisted only of the PHQ-9 and Kessler Psychological Distress Scale [K-10; (Kessler et al., 2002)] questionnaires. Participants of both groups were monitored and received weekly check-in telephone calls from a trained bachelor-level research assistant. These calls followed a script and were limited to 3–5 min. Completing the programs was self-paced, except that participants had to wait at least five days between consecutive lessons and complete all lessons within 10 weeks. A 10-week duration was provided to participants to complete the program instead of the previously-used 8-week period, in an attempt to maximize retention for this neuroimaging

study (i.e. setting a slightly more lenient time frame for participants to complete all 6 lessons).

Measures

Snaith–Hamilton Pleasure Scale (SHAPS)

The SHAPS is a well-established self-report questionnaire that assesses anhedonia via four domains of hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink (Snaith et al., 1995). It is composed of 14 statements of hedonic response in pleasurable situations that participants can either agree or disagree with based on their experience in the last few days (for example, 'I would enjoy my favorite television or radio program'). Scores on the SHAPS can range from 14 to 56, with higher scores corresponding to higher levels of anhedonia (Franken, Rassin, & Muris, 2007). The SHAPS was completed during pre-treatment and post-treatment visits with changes in anhedonia levels calculated by subtracting participants' pre-treatment from post-treatment scores. Accordingly, negative delta SHAPS scores indicate reduced anhedonia severity over time (i.e. better treatment outcome).

Monetary incentive delay (MID) task

The MID task has been used extensively to assess reward circuit activation and connectivity patterns among healthy as well as MDD populations (Admon et al., 2015b, 2017; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Pizzagalli et al., 2009; Wilson et al., 2018). The current version of the task involved five blocks with 24 trials each, for a total of 120 trials. Trials began with a visual cue (1.5 s) indicating one of three potential outcomes (reward: +$; loss: −$; no incentive: 0$). After a variable inter-stimulus-interval (3–7.5 s), a red target square was briefly presented (0.15 s). Participants responded to the square by pressing a button as quickly as possible. After a second delay (4.4–8.9 s), visual feedback (1.5 s) was displayed to indicate one of three potential trial outcomes (gain, penalty, neutral). A variable interval (3–12 s) separated the trials.

MRI data acquisition and processing

MRI data were acquired pre- and post-treatment at the McLean Imaging Center using a 3.0 Tesla Siemens TIM Trio MRI scanner fitted with a quadrature RF head coil. Functional scans involved the following parameters: TR = 2500 ms, TE = 35 ms, flip angle = 90°, FOV = 200, matrix 64 × 64 with 39 transverse 5-mm slices, providing an in-plane resolution of 3.125 × 3.125 × 5 mm. In addition, structural T1-weighted three-dimensional magnetization prepared rapid acquisition gradient-echo images were collected with the following parameters: TR = 2100 ms, TE = 2.25 ms, flip angle = 12°, FOV = 200, matrix 256 × 256 with 176 sagittal slices, providing an in-plane resolution of 1 mm^3.

fMRI data preprocessing using Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/software/) included co-registration of functional and anatomical images, segmentation, nonlinear volume-based spatial normalization [using Montreal Neurological Institute (MNI) space], and spatial smoothing with a Gaussian filter (6-mm full width at half maximum). The Artifact Detection Tool (ART; http://web.mit.edu/swg/software.htm) was used to identify and exclude outlier time points based on global mean image time series (threshold: 3 standard deviations from the mean) and movement (threshold: 0.7 mm; measured as scan-to-scan movement, separately for translation and rotation) parameters. Hemodynamic responses

were modeled using a canonical hemodynamic response function that was convolved with the onset times of task regressors to compute a general linear model (GLM) at the single-subject level. The GLM included seven task-related regressors: three cues (reward, penalty, no-incentive), three feedback types [reward (reward outcome following reward cue), no loss (no-change outcome following penalty cue), and neutral (no-change outcome following no-incentive cue)] and target. The feedback types of no change outcomes following reward cue and penalty outcome following penalty cue were rarely displayed and thus their appearance times were combined with no-response trials to form a single nuisance regressor in the GLM. The GLM also included high-pass temporal filtering (0.008 Hz), seven rigid-body movement parameters and ART outlier time points.

Pre- and post-treatment reward circuit activation were assessed using whole brain and region-of-interest (ROI) analyses. The ROI approach was focused on four key structures of the reward circuit that previously have shown altered reactivity in response to reward in MDD and have also been previously associated with treatment response in MDD, including the Nacc, putamen, caudate, and sgACC (Dunlop et al., 2017; Guo et al., 2016; Nakamura et al., 2021; Narushima et al., 2010; Wang et al., 2019). For the Nacc, caudate, and putamen, masks were defined using a manually segmented MNI-152 brain (Admon et al., 2015a; Admon et al., 2017). The sgACC mask was defined using the 'subgenual ACC' region from the Automated anatomical labeling atlas 3 (Rolls, Huang, Lin, Feng, & Joliot, 2020). MarsBAR toolbox v.044 (http://marsbar.sourceforge.net) was used to extract mean beta-estimates (activations) from these four ROIs for reward anticipation, reward feedback and neutral feedback task regressors. Analyses were focused on the response to reward (anticipation or feedback) *v.* baseline in order to associate given results to the reward condition. The neutral condition was controlled for in these analyses to account for matched cognitive processes. Generalized psychophysiological interaction (gPPI) analyses were also conducted in order to assess pre- to post-treatment changes in functional connectivity of the same four ROIs in response to reward feedback. For each participant, single-subject GLMs were constructed as described earlier, with the addition of the bilateral seed time course as a regressor and an additional PPI regressor (the interaction of the seed time course with the regressors for reward feedback). This interaction regressor is orthogonal to the task and seed regressors and describes the contribution of the interaction above and beyond the main effects of the task and seed time course. In addition, the orthogonality of the task and PPI regressors ensures that seed ROI activation and PPI connectivity are independent (McLaren et al., 2012).

Statistical analyses

Pre- and post-treatment SHAPS scores were entered into mixed ANOVA analyses with *Time* (pre-, post-treatment) as a within-subject factor and *Group* (iCBT, MAC, HC) as a between-subject factor. One MAC group participant was excluded from this analysis due to missing data. For each ROI, mean activation values for reward cue (anticipation) and reward feedback were separately entered into a mixed ANOVA analysis with *Time* (pre-, post-treatment) as a within-subject factor and *Group* (iCBT, MAC, HC) as a between-subject factor. For regions where a significant interaction emerged (Nacc and sgACC), a second ANOVA was conducted with feedback *Type* (reward, neutral) as an additional within-subject variable to better pinpoint the source of the effect.
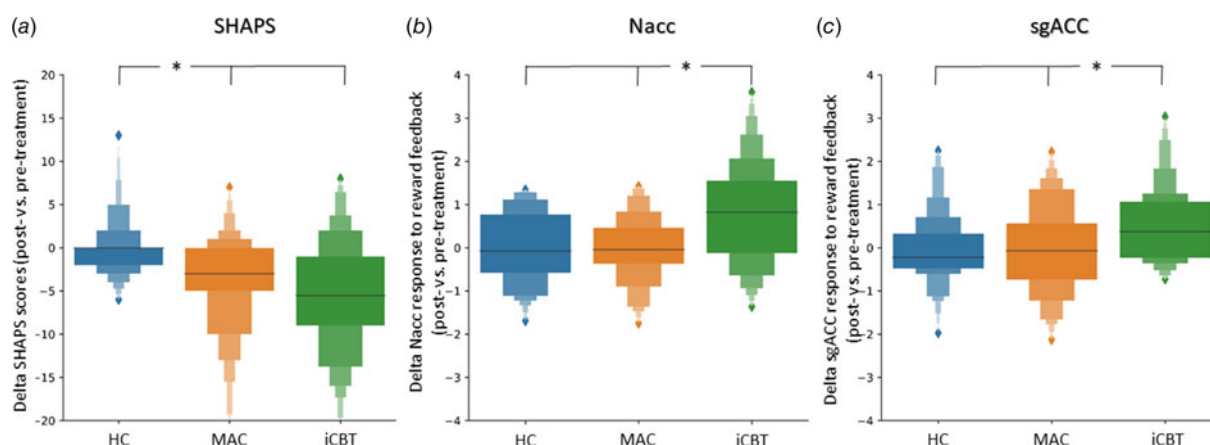
Fig. 1. Pre- to post-treatment changes in anhedonia severity and reward circuit activation. (*a*) Changes in SHAPS scores from pre- to post-treatment, with negative scores indicating a reduction in anhedonia severity post-treatment. Both MAC and iCBT groups exhibited a significant reduction in anhedonia severity post-treatment. (*b* & *c*) Changes in Nacc and sgACC activation, respectively, in response to reward feedback from pre- to post-treatment, with positive scores indicating enhanced reward reactivity post-treatment. Only the iCBT group exhibited a significant increase in reward reactivity post-treatment. * $p < 0.01$; HC, Healthy Control; MAC, Monitored Attention Control; iCBT, Internet-based cognitive-behavioral therapy; SHAPS, Snaith Hamilton Pleasure Scale; Nacc, nucleus accumbens; sgACC, subgenual anterior cingulate cortex.

Five participants were excluded from these analyses due to missing data in the Nacc (4 HC, 1 MAC) and three in the sgACC (1 HC, 2 iCBT). To account for the putative impact of age and sex on the response to treatment and on neural reactivity in MDD, ANOVAs assessing pre- and post-treatment SHAPS and reward circuit activation were repeated with age and sex as covariates. Whole brain analyses assessed changes in activation separately in response to reward anticipation and reward feedback from pre- to post-treatment using mixed ANOVA with *Time* (pre-, post-treatment) as a within-subject factor and *Group* (iCBT, MAC, HC) as a between-subject factor, while controlling for false-positive findings using a significance threshold of $p < 0.05$ family-wise error (FWE) corrected. Associations between pre- to post-treatment changes in SHAPS scores and changes in Nacc and sgACC reward activation were assessed separately for the iCBT and MAC groups using hierarchical linear regression. In each group, separate regression models for each ROI assessed the associations between changes from pre- to post-treatment in SHAPS scores and in Nacc or sgACC reward feedback activation, while controlling for changes in ROIs activation to neutral feedback. Specifically, in the first step, the change from pre- to post-treatment in activation in response to neutral was entered, and in the second step, the change from pre- to post-treatment in activation in response to reward was entered. Changes from pre- to post-treatment were calculated by subtracting pre-treatment values from post-treatment values, such that negative SHAPS change scores indicate a reduction in anhedonia severity post-treatment and positive neural reactivity scores indicate enhanced reward activation post-treatment. Furthermore, mediation analyses were conducted separately for each ROI in order to examine whether changes in activation from pre- to post-treatment mediated the association between group (iCBT *v.* MAC) and change in SHAPS scores. Mediation analyses were conducted using AMOS version 27 (IBM Corporation, USA) with bias-corrected bootstrapping of 2000 samples. Finally, gPPI analyses were performed among participants in the iCBT and MAC groups to assess pre- to post-treatment changes in functional connectivity strength between the two ROIs that enhanced their activity from pre- to post-treatment in response to reward feedback (Nacc and

sgACC). In these analyses the Nacc was treated as the seed. False-positive findings were controlled by applying small volume correction using family-wise error (FWE) correction within the sgACC mask. Exploratory whole-brain analysis further assessed changes in ROI connectivity in response to reward anticipation and reward feedback from pre- to post-treatment using mixed ANOVA with *Time* (pre-, post-treatment) as a within-subject factor and *Group* (iCBT, MAC, HC) as a between-subject factor. These analyses were focused on *Group* by *Time* interactions, while controlling for false-positive findings using a significance threshold of $p < 0.05$ family-wise error (FWE) corrected.

Results

Pre- to post-treatment changes in anhedonia severity

The mixed ANOVA on SHAPS scores with *Time* and *Group* as factors yielded a main effect of *Group* ($F_{(2,90)} = 87.50$, $p < 0.001$) due to overall lower SHAPS scores (lower anhedonia severity) for the HC group compared to both MDD groups. In addition, there was a significant a main effect of *Time* ($F_{(1,90)} = 30.35$, $p < 0.001$), due to overall lower SHAPS scores post- compared to pre-treatment. Critically, a significant *Group* by *Time* interaction also emerged ($F_{(1,90)} = 8.15$, $p = 0.001$), driven by a decrease in SHAPS scores (reduced anhedonia severity) post- compared to pre-treatment for the two MDD patient groups but not for the HC group (post-hoc: iCBT: $t_{(25)} = -3.93$, $p = 0.001$; MAC: $t_{(24)} = -2.98$, $p = 0.006$; HC: $t_{(41)} = -0.55$, $p = 0.563$; Figure 1*a*). Repeating the same analyses while controlling for age and sex yielded similar results [main effect of *Group* ($F_{(2,84)} = 75.59$, $p < 0.001$), main effect of *Time* ($F_{(2,84)} = 5.52$, $p = 0.028$), *Group* by *Time* interaction ($F_{(2,84)} = 7.29$, $p = 0.001$)].

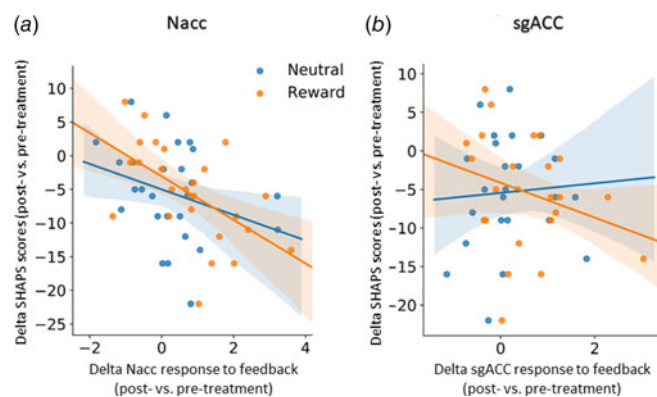### Pre- to post-treatment changes in reward circuit activation

Separate *Time* × *Group* ANOVAs on reward feedback activation for each ROI revealed a significant *Group* by *Time* interaction only for the Nacc and the sgACC (Nacc: $F_{(2,86)} = 5.07$, $p = 0.008$; sgACC: $F_{(2,88)} = 3.40$, $p = 0.038$; caudate: $F_{(2,91)} = 0.30$, $p = 0.744$;
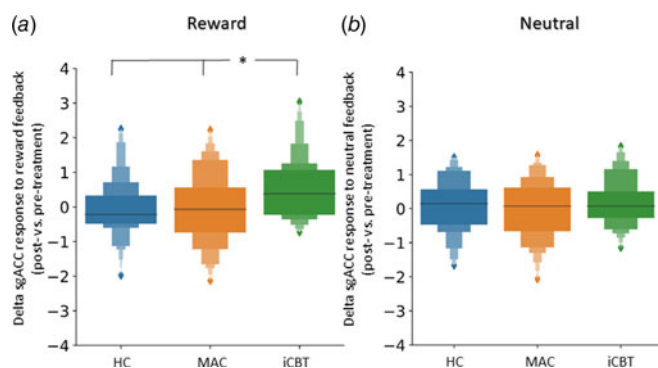
Fig. 2. Pre- to post-treatment changes in sgACC activation by feedback type. Changes in sgACC activation in response to (*a*) reward and (*b*) neutral feedback from pre- to post-treatment, with positive scores indicating enhanced reward reactivity post-treatment. Only the iCBT group exhibited a significant increase in sgACC activation, and this increased activation was specific to reward feedback. * $p < 0.01$; HC, Healthy Control; MAC, Monitored Attention Control; iCBT, Internet-based cognitive-behavioral therapy; sgACC, subgenual anterior cingulate cortex.

Fig. 3. Associations between changes in anhedonia severity and reward circuit activation following iCBT. Changes in SHAPS scores from pre- to post-treatment in the iCBT group were negatively associated with changes in (*a*) Nacc and (*b*) sgACC activation in responses to reward feedback from pre- to post-treatment, while controlling for the change in response to neutral feedback. In other words, reduced anhedonia following iCBT treatment was specifically associated with enhanced reward reactivity. iCBT, Internet-based cognitive-behavioral therapy; SHAPS, Snaith Hamilton Pleasure Scale; Nacc, nucleus accumbens; sgACC, subgenual anterior cingulate cortex.

putamen: $F_{(2,91)} = 0.57$, $p = 0.568$). Accordingly, further analyses were pursued only with respect to Nacc and sgACC activation. Within the Nacc and sgACC, these interactions were driven by enhanced responses to reward feedback post- compared to pre-treatment in the iCBT group only (post-hoc: Nacc: iCBT: $t_{(25)} = 3.05$, $p = 0.005$; MAC: $t_{(29)} = 0.19$, $p = 0.855$; HC: $t_{(36)} = 0.12$, $p = 0.906$; sgACC: iCBT: $t_{(23)} = 2.84$, $p = 0.009$; MAC: $t_{(24)} = 0.29$, $p = 0.977$; HC: $t_{(39)} = -0.43$, $p = 0.669$; Figure 1*b* & *c*). Visual inspection of these data points raised the possibility of potential group differences in the magnitude of variability with respect to Nacc activation, yet a Levene's test showed that the variance in Nacc response to reward feedback was not significantly different across groups ($F_{(2,85)} = 2.82$, $p = 0.065$). Repeating the same analyses with reward and neutral feedback *Type* as an additional within-subject factor revealed a significant three-way *Group* by *Time* by *Type* interaction for the sgACC ($F_{(2,88)} = 4.09$, $p = 0.020$) but not for the Nacc ($F_{(2,86)} = 0.70$, $p = 0.501$). Post-hoc analysis revealed that this effect was driven by significant pre- to post-treatment changes in sgACC activation in the iCBT group in response to reward but not neutral feedback (post-hoc: sgACC reward iCBT: $t_{(23)} = 2.84$, $p = 0.009$; sgACC neutral iCBT: $t_{(23)} = 1.21$, $p = 0.239$; Figure 2). Repeating the same analyses while controlling for age and sex yielded similar results [*Group* by *Time* interaction (Nacc: $F_{(2,79)} = 3.74$, $p = 0.028$; sgACC: $F_{(2,81)} = 2.76$, $p = 0.07$; caudate: $F_{(2,84)} = 0.12$, $p = 0.891$; putamen: $F_{(2,84)} = 0.49$, $p = 0.618$), *Group* by *Time* by *Type* interaction (sgACC: $F_{(2,81)} = 4.22$, $p = 0.018$; Nacc: $F_{(2,79)} = 1.009$, $p = 0.369$)].

With respect to activation in response to reward anticipation, *Time* × *Group* ANOVAs revealed a significant main effect of *Time* due to reduced activation post-treatment compared to pre-treatment across all three groups in the Nacc ($F_{(1,82)} = 17.008$, $p < 0.001$) and Putamen ($F_{(1,87)} = 11.202$, $p = 0.001$). Contrary to our hypotheses, no significant *Group* by *Time* interactions emerged in any of the four ROIs (Nacc: $F_{(2,85)} = 1.26$, $p = 0.289$; sgACC: $F_{(2,86)} = 1.426$, $p = 0.246$; caudate: $F_{(2,88)} = 0.032$, $p = 0.968$; putamen: $F_{(2,90)} = 1.156$, $p = 0.319$). Thus, further analyses were not conducted with respect to reward anticipation. Lastly, whole-brain analysis revealed a single cluster, located in the left dorsal posterior cingulate cortex ($x = -15$ $y = -25.46$ $z = 38.41$; Brodmann 31) that exhibited a significant main effect of *Time* due to overall

reduced activation to reward feedback post- compared to pre-treatment across groups ($F_{(1,86)} = 35.82$, $p < 0.001$). No other regions emerged with respect to the main effect of *Group* or a *Group* by *Time* interaction at a significance threshold of $p < 0.05$ whole brain FWE corrected.

Associations between changes in anhedonia severity and reward circuit activation

Hierarchical linear regression controlling for changes in response to neutral feedback, revealed that, in the iCBT group, enhanced responses in the Nacc and sgACC to reward feedback post- compared to pre-treatment were associated with a stronger decrease in SHAPS scores (reduced anhedonia severity) post- compared to pre-treatment (Nacc: $F_{\text{Change}(1,23)} = 7.938$, $R^2_{\text{Change}} = 0.233$, $p = 0.01$; sgACC: $F_{\text{Change}(1,21)} = 6.057$, $R^2_{\text{Change}} = 0.223$, $p = 0.023$; Figure 3). Repeating the same analysis in the MAC group yielded no significant associations (Nacc: $F_{\text{Change}(1,21)} = 0.400$, $R^2_{\text{Change}} = 0.019$, $p = 0.534$; sgACC: $F_{\text{Change}(1,22)} = 0.682$, $R^2_{\text{Change}} = 0.030$, $p = 0.418$). Critically, mediation analyses revealed that the change from pre- to post-treatment in Nacc reward feedback activation mediated the relation between group (iCBT *v.* MAC) and change in SHAPS scores (Beta = -1.847, 95% CI -4.067 to -0.472, $p = 0.004$). Repeating the same analyses with respect to change in sgACC activation yielded a non-significant effect (Beta = -0.431, 95% CI -2.181 to 0.286, $p = 0.236$).

Pre- to post- iCBT changes in reward circuit connectivity

PPI analysis focusing on pre- to post-treatment changes in Nacc-sgACC functional connectivity in the iCBT group revealed a single cluster within the sgACC that increased its functional connectivity with the Nacc in response to reward feedback post- compared to pre-treatment ($t = 3.26$, $p < 0.05$ FWE corrected; cluster size = 24 voxels; Figure 4). Repeating the same analysis for the MAC group yielded no clusters within the sgACC that exhibited significant changes in functional connectivity with the Nacc. Lastly, whole-brain analysis revealed no clusters that exhibited a *Group* by *Time* interaction with respect to connectivity
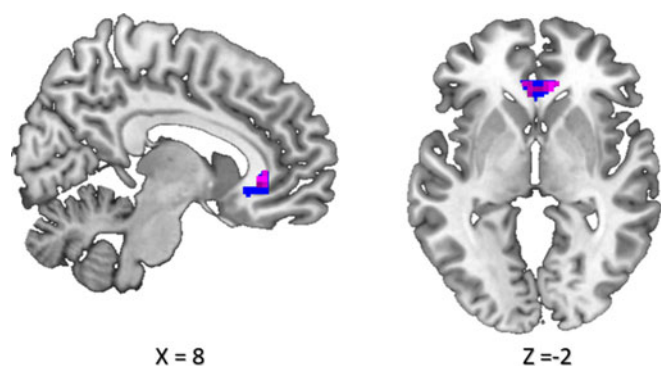
Fig. 4. Changes in reward circuit connectivity following iCBT. In pink is a cluster (cluster size = 24 voxels) within the sgACC mask (blue) that showed increased functional connectivity with the Nacc in response to reward feedback in the iCBT group post-compared to pre-treatment. iCBT, Internet-based cognitive-behavioral therapy; Nacc, nucleus accumbens; sgACC, subgenual anterior cingulate cortex.

patterns in response to reward feedback at a significance threshold of $p < 0.05$ whole-brain FWE corrected.

Discussion

The goal of the present study was to examine whether iCBT for depression results in reduced anhedonia severity and enhanced reward circuit activation and connectivity, and whether these two effects are related. Findings suggest that a 10-week long technician-assisted iCBT treatment program indeed reduced self-reported anhedonia, but that this effect was also present in patients undergoing a monitored attention control (i.e. MAC) program. At the neural level, iCBT, but not MAC, resulted in enhanced Nacc and sgACC activation in response to reward feedback, and enhanced Nacc-sgACC functional connectivity in response to reward feedback. Finally, enhanced Nacc and sgACC activation in response to reward feedback was associated with reduced anhedonia following iCBT, with enhanced Nacc activation also mediating the reduction in anhedonia severity post-treatment. Contrary to our expectations, no significant group effects emerged when considering a neural response to reward anticipation.

Prior work has documented the efficacy of iCBT in reducing depressive symptoms in MDD patients and in improving remission rates (Batterham et al., 2021; Josephine et al., 2017; Sander, Rausch, & Baumeister, 2016). Our results add to this literature by showing, we believe for the first time, that iCBT is also associated with reduced anhedonia severity as well as potentiation of key nodes within the brain reward system. Considering that anhedonia is a common transdiagnostic feature across several mental disorders beyond MDD, including posttraumatic stress disorder, anxiety disorders, and schizophrenia, the current results point towards the possible efficacy of iCBT in aiding patients with these disorders as well, in accordance with previous literature (Sander et al., 2016). It should be noted, however, that reduced anhedonia severity was also evident among MDD patients following 10 weeks of a control (MAC) program. This result is surprising considering that within this cohort, patients completing the iCBT program were found to exhibit lower depression severity and higher remission rates compared to patients completing the MAC program (Rosso et al., 2017). This effect could have been driven by spontaneous fluctuations in anhedonia over time; by nonspecific factors that were also present in the MAC program

such as encounters with study staff throughout multiple in-person study visits and weekly phone contact with study staff during the 10-week treatment period; or due to the positive impact of anticipation to start the iCBT program following MAC completion.

In contrast, fMRI analyses indicated that only the iCBT treatment program yielded an increase in reward circuit activation in response to reward, an effect that was not found following MAC or in the healthy control group. Within the reward circuit, the Nacc and sgACC demonstrated elevated activation following iCBT, with the latter being specific to reward feedback and the former present for both reward and neutral feedback. These two regions also exhibited enhanced functional connectivity with each other in response to reward feedback following iCBT but not following MAC. Furthermore, enhanced reward activation in the Nacc and sgACC following iCBT was associated with reduced anhedonia severity post-treatment. Finally, changes in Nacc reward feedback activation following iCBT mediated the relation between the treatment group (iCBT v. MAC) and changes in anhedonia severity. Taken together, these findings extend prior reports highlighting enhanced reward circuit activation and connectivity in depression following various treatment modalities, including antidepressants (Heller et al., 2013; Takamura et al., 2017), DBS (Conen et al., 2018; Schlaepfer et al., 2008), and psychotherapy (Yoshimura et al., 2014). Critically, in most of these studies, improvement in clinical outcome and reduction in anhedonic symptom severity following treatment was positively associated with enhanced reward circuit reactivity, an effect that was also found in the current cohort following iCBT. This may suggest that improved clinical outcome in the form of reduced anhedonia severity following treatment in depression is accompanied by enhancement of reward circuit activation and connectivity, and furthermore, that these neural modifications represent a common therapeutic pathway in depression across treatment modalities. Identifying the treatment modality that would most efficiently enhance each patient's reward circuit reactivity could therefore represent an important step towards individually tailored treatment selection in MDD, as well as in other anhedonia-related mental disorders.

The fact that enhanced reward activation following treatment was found in ventral sections of the striatum (Nacc) but not in more dorsal sections (caudate, putamen) mirrors previous findings implicating the ventral striatum as a key structure associated with anhedonia (Der-Avakian & Markou, 2012; Keller et al., 2013; Takamura et al., 2017). Moreover, reduced ventral striatum response to reward has been suggested to represent a specific indicator of anhedonia rather than a marker of MDD in general (Takamura et al., 2017), which is further consistent with current results. Identifying brain regions that are uniquely associated with anhedonia may inform treatment modalities that require specific neural targets, such as deep transcranial magnetic stimulation (TMS), DBS, and neurofeedback (Auerbach, Admon, & Pizzagalli, 2014; Pizzagalli, 2011). Also of relevance is the characterization of neural markers that predict treatment response. In this respect, it is interesting to note that prior work has emphasized the rostral ACC (rACC) as a treatment-related outcome predictor. Specifically, increased pre-treatment rACC activity emerged as a marker of treatment response in depression (Pizzagalli, 2011). Even within this cohort, larger pre-treatment rACC volume was positively associated with greater depressive symptom improvement post-treatment (Webb et al., 2018). On the other hand, the results of the current study add to growing literature that points towards the sgACC as a brain region that

exhibits plasticity following treatment. Nevertheless, it is important to note that mixed results were reported in the literature with respect to the direction of the change in sgACC activation following treatment (Siegle et al., 2012; Straub et al., 2015). Additional studies should address this gap in order to improve our understanding regarding the role of the sgACC and its plasticity in depression and its treatment.

While the current results provide novel insights on the neural impact of iCBT in depression, several limitations should be acknowledged. First, the neural response to reward anticipation was not related to the treatment group. This is surprising considering that previous work highlighted neural impairments in MDD in the context of both reward anticipatory and reward consummatory processes (Borsini, Wallis, Zunszain, Pariante, & Kempton, 2020). In fact, connectivity alterations in response to anticipatory processing were shown to predict antidepressant treatment response in MDD (Walsh et al., 2017). We can speculate that the current results may relate to our longitudinal design and stem from the stronger impact of habituation processes on neural anticipatory response compared to the consummatory response. Indeed, the neural response to reward anticipation in the Nacc, putamen, and caudate decreased over time across groups in the current sample. Hence, habituation processes might have limited our ability to detect treatment effects during the anticipation phase. Future longitudinal studies may address this issue by implementing slightly different tasks across time points to lessen any putative habituation effects. Second, due to the relatively modest size of each group in our sample, we did not account for different subtypes of depression. Thus, we could not assess whether iCBT is particularly beneficial for a form of depression marked by pronounced anhedonia. This limitation may further explain the lack of group differences in anhedonia reduction following iCBT *v.* MAC programs. Also, due to sample size considerations, Nacc-sgACC connectivity changes were tested separately for the iCBT and MAC groups, and hence changes in iCBT group connectivity patterns cannot be interpreted as an indication of group interaction. Third, iCBT as implemented in this study does not target anhedonic symptoms specifically but rather depressive symptoms more broadly. Extending these findings to forms of CBT that do specifically target positive affect (e.g. Craske et al., 2019) would be an important future direction. Fourth, in the absence of an additional follow-up MRI scan, we cannot determine whether neural changes in reward circuitry from pre- to post-treatment were sustained over time. Future work should therefore include follow-up assessments designed to evaluate whether the abovementioned enhanced reward circuit activation and connectivity are retained in the long term, and whether the association with anhedonia severity holds.

In conclusion, the current study investigated whether iCBT results in reduced anhedonia among depressed patients, and whether these therapeutic effects are accompanied by enhancement of reward circuit activation and connectivity. Results indicate that following iCBT, but not a monitored control condition, depressed individuals exhibited enhanced reward circuit activation and connectivity, and that such enhancement was positively associated with, and in fact mediated, the reduction in anhedonia severity following treatment. These findings suggest that improved clinical outcome in the form of reduced anhedonia severity may stem from enhanced reward circuit responsivity following iCBT treatment. In light of similar findings from other treatment modalities, these neural modifications may represent a common therapeutic pathway in depression across modalities.

References

Admon, R., Holsen, L. M., Aizley, H., Remington, A., Whitfield-Gabrieli, S., Goldstein, J. M., & Pizzagalli, D. A. (2015a). Striatal hypersensitivity during stress in remitted individuals with recurrent depression. *Biological Psychiatry*, 78(1), 67–76. https://doi.org/10.1016/j.biopsych.2014.09.019.

Admon, R., Kaiser, R. H., Dillon, D. G., Beltzer, M., Goer, F., Olson, D. P., … Pizzagalli, D. A. (2017). Dopaminergic enhancement of striatal response to reward in major depression. *American Journal of Psychiatry*, 174(4), 378–386. https://doi.org/10.1176/appi.ajp.2016.16010111.

Admon, R., Nickerson, L. D., Dillon, D. G., Holmes, A. J., Bogdan, R., Kumar, P., … Pizzagalli, D. A. (2015b). Dissociable cortico-striatal connectivity abnormalities in major depression in response to monetary gains and penalties. *Psychological Medicine*, 45(1), 121–131. https://doi.org/10.1017/S0033291714001123.

Admon, R., & Pizzagalli, D. A. (2015). Corticostriatal pathways contribute to the natural time course of positive mood. *Nature Communications*, 6 (May), 1–11. https://doi.org/10.1038/ncomms10065.

Alexander, L., Gaskin, P. L. R., Sawiak, S. J., Fryer, T. D., Hong, Y. T., Cockcroft, G. J., … Roberts, A. C. (2019). Fractionating blunted reward processing characteristic of anhedonia by over-activating primate subgenual anterior cingulate cortex. *Neuron*, 101(2), 307–320.e6. https://doi.org/10.1016/j.neuron.2018.11.021.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th Text Revision ed.). Washington, DC: American Psychiatric Association.

Auerbach, R. P., Admon, R., & Pizzagalli, D. A. (2014). Adolescent depression: Stress and reward dysfunction. *Harvard Review of Psychiatry*, 22(3), 139–148. https://doi.org/10.1097/HRP.0000000000000034.

Azab, H., & Hayden, B. Y. (2018). Correlates of economic decisions in the dorsal and subgenual anterior cingulate cortices. *The European Journal of Neuroscience*, 47(8), 979–993. https://doi.org/10.1111/ejn.13865.

Batterham, P. J., Calear, A. L., Farrer, L., Gulliver, A., & Kurz, E. (2021). Efficacy of a transdiagnostic self-help internet intervention for reducing depression, anxiety, and suicidal ideation in adults: Randomized controlled trial. *Journal of Medical Internet Research*, 23(1), e22698.

Borsini, A., Wallis, A. S. J., Zunszain, P., Pariante, C. M., & Kempton, M. J. (2020). Characterizing anhedonia: A systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cognitive,*

Affective & Behavioral Neuroscience, 20(4), 816–841. https://doi.org/10.3758/s13415-020-00804-6.

Boumparis, N., Karyotaki, E., Kleiboer, A., Hofmann, S. G., & Cuijpers, P. (2016). The effect of psychotherapeutic interventions on positive and negative affect in depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, 202, 153–162. https://doi.org/10.1016/j.jad.2016.05.019.

Conen, S., Matthews, J. C., Patel, N. K., Anton-Rodriguez, J., & Talbot, P. S. (2018). Acute and chronic changes in brain activity with deep brain stimulation for refractory depression. *Journal of Psychopharmacology*, 32(4), 430–440. https://doi.org/10.1177/0269881117742668.

Cooper, J. A., Arulpragasam, A. R., & Treadway, M. T. (2018). Anhedonia in depression: Biological mechanisms and computational models. *Current Opinion in Behavioral Sciences*, 22, 128–135. https://doi.org/10.1016/j.cobeha.2018.01.024.

Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., Dour, H., & Rosenfield, D. (2019). Positive affect treatment for depression and anxiety: A randomized clinical trial for a core feature of anhedonia. *Journal of Consulting and Clinical Psychology*, 87(5), 457–471. https://doi.org/10.1037/ccp0000396.

Cuijpers, P., Karyotaki, E., Ciharova, M., Miguel, C., Noma, H., & Furukawa, T. A. (2021). The effects of psychotherapies for depression on response, remission, reliable change, and deterioration: A meta-analysis. *Acta Psychiatrica Scandinavica*, 144(3), 288–299. https://doi.org/10.1111/acps.13335.

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences*, 35(1), 68–77. https://doi.org/10.1016/j.tins.2011.11.005.

Dunlop, B. W., Rajendra, J. K., Craighead, W. E., Kelley, M. E., McGrath, C. L., Choi, K. S., … Mayberg, H. S. (2017). Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. *The American Journal of Psychiatry*, 174(6), 533–545. https://doi.org/10.1176/appi.ajp.2016.16050518.

Etzelmueller, A., Vis, C., Karyotaki, E., Baumeister, H., Titov, N., Berking, M., … Ebert, D. D. (2020). Effects of internet-based cognitive-behavioral therapy in routine care for adults in treatment for depression and anxiety: Systematic review and meta-analysis. *Journal of Medical Internet Research*, 22(8), e18100. https://doi.org/10.2196/18100.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., … Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Medicine*, 10(11), e1001547.

Franken, I. H. A., Rassin, E., & Muris, P. (2007). The assessment of anhedonia in clinical and non-clinical populations: Further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). *Journal of Affective Disorders*, 99(1–3), 83–89. https://doi.org/10.1016/j.jad.2006.08.020.

Furukawa, T. A., Karyotaki, E., Suganuma, A., Pompoli, A., Ostinelli, E. G., Cipriani, A., … Efthimiou, O. (2018). Dismantling, personalising and optimising internet cognitive-behavioural therapy for depression: A study protocol for individual participant data component network meta-analysis. *BMJ Open*, 8(11), 1–9. https://doi.org/10.1136/bmjopen-2018-026137.

Gabbay, V., Ely, B. A., Li, Q., Bangaru, S. D., Panzer, A. M., Alonso, C. M., … Milham, M. P. (2013). Striatum-based circuitry of adolescent depression and anhedonia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52(6), 628–641.e13. https://doi.org/10.1016/j.jaac.2013.04.003.

Gaynes, B. N., Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Spencer, D., & Fava, M. (2008). The STAR*D study: Treating depression in the real world. *Cleveland Clinic Journal of Medicine*, 75(1), 57–66. https://doi.org/10.3949/ccjm.75.1.57.

Greenberg, P. E., Fournier, A. A., Sisitsky, T., Pike, C. T., & Kessler, R. C. (2015). The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *Journal of Clinical Psychiatry*, 76(2), 155–162. https://doi.org/10.4088/JCP.14m09298.

Guo, C. C., Hyett, M. P., Nguyen, V. T., Parker, G. B., & Breakspear, M. J. (2016). Distinct neurobiological signatures of brain connectivity in depression subtypes during natural viewing of emotionally salient films. *Psychological Medicine*, 46(7), 1535–1545. https://doi.org/10.1017/S0033291716000179.

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, 35(1), 4–26. https://doi.org/10.1038/npp.2009.129.

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology*, 29(10), 1765–1781. https://doi.org/10.1038/sj.npp.1300506.

Heller, A. S., Johnstone, T., Light, S. N., Peterson, M. J., Kolden, G. G., Kalin, N. H., & Davidson, R. J. (2013). Relationships between changes in sustained fronto-striatal connectivity and positive affect in major depression resulting from antidepressant treatment. *American Journal of Psychiatry*, 170(2), 197–206. https://doi.org/10.1176/appi.ajp.2012.12010014.

Höflich, A., Michenthaler, P., Kasper, S., & Lanzenberger, R. (2018). Circuit mechanisms of reward, anhedonia, and depression. *International Journal of Neuropsychopharmacology*, 22(2), 105–118. https://doi.org/10.1093/ijnp/pyy081.

Josephine, K., Josefine, L., Philipp, D., David, E., & Harald, B. (2017). Internet- and mobile-based depression interventions for people with diagnosed depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, 223, 28–40. https://doi.org/10.1016/j.jad.2017.07.021.

Karyotaki, E., Efthimiou, O., Miguel, C., Bermpohl, F. M. G., Furukawa, T. A., Cuijpers, P., … Gemmil, A. W. (2021). Internet-based cognitive-behavioral therapy for depression: A systematic review and individual patient data network meta-analysis. *JAMA Psychiatry*, 78(4), 361–371.

Kaur, M., & Sanches, M. (2021). Experimental therapeutics in treatment-resistant major depressive disorder. *Journal of Experimental Pharmacology*, 13, 181–196. https://doi.org/10.2147/JEP.S259302.

Keller, J., Young, C. B., Kelley, E., Prater, K., Levitin, D. J., & Menon, V. (2013). Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. *Journal of Psychiatric Research*, 47(10), 1319–1328. https://doi.org/10.1016/j.jpsychires.2013.05.015.

Keren, H., O'Callaghan, G., Vidal-Ribas, P., Buzzell, G. A., Brotman, M. A., Leibenluft, E., … Stringaris, A. (2018). Reward processing in depression: A conceptual and meta-analytic review across fMRI and EEG studies. *American Journal of Psychiatry*, 175(11), 1111–1120. https://doi.org/10.1176/appi.ajp.2018.17101124.

Kessler, R. C., Andrews, G., Colpe, L. J., Hiripi, E., Mroczek, D. K., Normand, S. L. T., … Zaslavsky, A. M. (2002). Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychological Medicine*, 32(6), 959–976. https://doi.org/10.1017/s0033291702006074.

Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2008). Neural responses to monetary incentives in major depression. *Biological Psychiatry*, 63(7), 686–692. https://doi.org/10.1016/j.biopsych.2007.07.023.

Knutson, B., Westdorp, A., Kaiser, E., & Hommer, D. (2000). FMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage*, 12(1), 20–27. https://doi.org/10.1006/nimg.2000.0593.

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9. *Journal of General Internal Medicine*, 16(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Lopez, A. D., & Murray, C. C. J. L. (1998). The global burden of disease, 1990–2020. *Nature Medicine*, 4(11), 1241–1243. https://doi.org/10.1038/3218.

Mclaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. *Neuroimage*, 61, 1277–1286.

Moitra, M., Santomauro, D., Degenhardt, L., Collins, P. Y., Whiteford, H., Vos, T., & Ferrari, A. (2021). Estimating the risk of suicide associated with mental disorders: A systematic review and meta-regression analysis. *Journal of Psychiatric Research*, 137(December 2020), 242–249. https://doi.org/10.1016/j.jpsychires.2021.02.053.

Nakamura, T., Tomita, M., Horikawa, N., Ishibashi, M., Uematsu, K., Hiraki, T., … Uchimura, N. (2021). Functional connectivity between the amygdala and subgenual cingulate gyrus predicts the antidepressant effects of ketamine in patients with treatment-resistant depression. *Neuropsychopharmacology Reports*, 41(2), 168–178. https://doi.org/10.1002/npr2.12165.

Narushima, K., McCormick, L. M., Yamada, T., Thatcher, R. W., & Robinson, R. G. (2010). Subgenual cingulate theta activity predicts treatment response of repetitive transcranial magnetic stimulation in participants with vascular

depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(1), 75–84. https://doi.org/10.1176/jnp.2010.22.1.75.

Nestler, E. J., & Carlezon, W. A. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry*, *59*(12), 1151–1159. https://doi.org/10.1016/j.biopsych.2005.09.018.

Nielson, D. M., Keren, H., O'Callaghan, G., Jackson, S. M., Douka, I., Vidal-Ribas, P., … Stringaris, A. (2021). Great expectations: A critical review of and suggestions for the study of reward processing as a cause and predictor of depression. *Biological Psychiatry*, *89*(2), 134–143. https://doi.org/10.1016/j.biopsych.2020.06.012.

Ormel, J., Kessler, R. C., & Schoevers, R. (2019). Depression: More treatment but no drop in prevalence: How effective is treatment? And can we do better? *Current Opinion in Psychiatry*, *32*(4), 348–354. https://doi.org/10.1097/YCO.0000000000000505.

Perini, S., Titov, N., & Andrews, G. (2009). Clinician-assisted internet-based treatment is effective for depression: Randomized controlled trial. *The Australian and New Zealand Journal of Psychiatry*, *43*(6), 571–578. https://doi.org/10.1080/00048670902873722.

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. *Neuropsychopharmacology*, *36*(1), 183–206.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*(1), 393–423. https://doi.org/10.1146/annurev-clinpsy-050212-185606.

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., … Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry*, *166*(6), 702–710. https://doi.org/10.1176/appi.ajp.2008.08081201.

Rizvi, S. J., Pizzagalli, D. A., Sproule, B. A., & Kennedy, S. H. (2016). Assessing anhedonia in depression: Potentials and pitfalls. *Neuroscience and Biobehavioral Reviews*, *65*, 21–35. https://doi.org/10.1016/j.neubiorev.2016.03.004.

Rolls, E. T., Huang, C.-C., Lin, C.-P., Feng, J., & Joliot, M. (2020). Automated anatomical labelling atlas 3. *NeuroImage*, *206*, 116189. https://doi.org/https://doi.org/10.1016/j.neuroimage.2019.116189.

Rosso, I. M., Killgore, W. D. S., Olson, E. A., Webb, C. A., Fukunaga, R., Auerbach, R. P., … Rauch, S. L. (2017). Internet-based cognitive behavior therapy for major depressive disorder: A randomized controlled trial. *Depression and Anxiety*, *34*(3), 236–245. https://doi.org/10.1002/da.22590.

Sander, L., Rausch, L., & Baumeister, H. (2016). Effectiveness of internet-based interventions for the prevention of mental disorders: A systematic review and meta-analysis. *JMIR Mental Health*, *3*, e38. https://doi.org/10.2196/mental.6061.

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., … Sturm, V. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*, *33*(2), 368–377. https://doi.org/10.1038/sj.npp.1301408.

Siegle, G. J., Thompson, W. K., Collier, A., Berman, S. R., Feldmiller, J., Thase, M. E., & Friedman, E. S. (2012). Toward clinically useful neuroimaging in depression treatment: Prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. *Archives of General Psychiatry*, *69*(9), 913–924. https://doi.org/10.1001/archgenpsychiatry.2012.65.

Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. *The British Journal of Psychiatry*, *167*(1), 99–103.

Strait, C. E., Sleezer, B. J., Blanchard, T. C., Azab, H., Castagno, M. D., & Hayden, B. Y. (2016). Neuronal selectivity for spatial positions of offers and choices in five reward regions. *Journal of Neurophysiology*, *115*(3), 1098–1111. https://doi.org/10.1152/jn.00325.2015.

Straub, J., Metzger, C. D., Plener, P. L., Koelch, M. G., Groen, G., & Abler, B. (2017). Successful group psychotherapy of depression in adolescents alters fronto-limbic resting-state connectivity. *Journal of Affective Disorders*, *209* (August 2016), 135–139. https://doi.org/10.1016/j.jad.2016.11.024.

Straub, J., Plener, P. L., Sproeber, N., Sprenger, L., Koelch, M. G., Groen, G., & Abler, B. (2015). Neural correlates of successful psychotherapy of depression in adolescents. *Journal of Affective Disorders*, *183*, 239–246. https://doi.org/10.1016/j.jad.2015.05.020.

Takamura, M., Okamoto, Y., Okada, G., Toki, S., Yamamoto, T., Ichikawa, N., … Yamawaki, S. (2017). Patients with major depressive disorder exhibit reduced reward size coding in the striatum. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *79*(June), 317–323. https://doi.org/10.1016/j.pnpbp.2017.07.006.

Titov, N., Andrews, G., Davies, M., Mcintyre, K., Robinson, E., & Solley, K. (2010). Internet treatment for depression: A randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*, *5*(6), 1–9. https://doi.org/10.1371/journal.pone.0010939.

Wacker, J., Dillon, D. G., & Pizzagalli, D. A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: Integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, *46*(1), 327–337. https://doi.org/10.1016/j.neuroimage.2009.01.058.

Walsh, E., Carl, H., Eisenlohr-Moul, T., Minkel, J., Crowther, A., Moore, T., … Dichter, G. S. (2017). Attenuation of frontostriatal connectivity during reward processing predicts response to psychotherapy in major depressive disorder. *Neuropsychopharmacology*, *42*(4), 831–843. https://doi.org/10.1038/npp.2016.179.

Wang, Q., Tian, S., Tang, H., Liu, X., Yan, R., Hua, L., … Yao, Z. (2019). Identification of major depressive disorder and prediction of treatment response using functional connectivity between the prefrontal cortices and subgenual anterior cingulate: A real-world study. *Journal of Affective Disorders*, *252*, 365–372. https://doi.org/10.1016/j.jad.2019.04.046.

Wang, S., Leri, F., & Rizvi, S. J. (2021). Anhedonia as a central factor in depression: Neural mechanisms revealed from preclinical to clinical evidence. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *110* (December 2020), 110289. https://doi.org/10.1016/j.pnpbp.2021.110289.

Webb, C. A., Dillon, D. G., Pechtel, P., Goer, F. K., Murray, L., Huys, Q. J., … Pizzagalli, D. A. (2016). Neural correlates of three promising endophenotypes of depression: Evidence from the EMBARC study. *Neuropsychopharmacology*, *41*(2), 454–463. https://doi.org/10.1038/npp.2015.165.

Webb, C. A., Olson, E. A., Killgore, W. D. S., Pizzagalli, D. A., Rauch, S. L., & Rosso, I. M. (2018). Rostral anterior cingulate cortex morphology predicts treatment response to internet-based cognitive-behavioral therapy for depression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(3), 255–262. https://doi.org/10.1016/j.bpsc.2017.08.005.

Wilson, R. P., Colizzi, M., Bossong, M. G., Allen, P., Kempton, M., & Bhattacharyya, S. (2018). The neural substrate of reward anticipation in health: A meta-analysis of fMRI findings in the monetary incentive delay task. *Neuropsychology Review*, *28*(4), 496–506. https://doi.org/10.1007/s11065-018-9385-5.

World Health Organization. (2017). *Depression and other common mental disorders: Global health estimates*. World Health Organization. Retrieved from https://apps.who.int/iris/handle/10665/254610.

Yang, Z., Oathes, D., Linn, K. A., Bruce, S. E., Satterthwaite, T. D., Cook, P. A., … Sheline, Y. I. (2018). Cognitive-behavioral therapy Is associated with enhanced cognitive control network activity in major depression and post-traumatic stress disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(4), 311–319. https://doi.org/10.1016/j.bpsc.2017.12.006.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., … Yamawaki, S. (2014). Cognitive-behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Social Cognitive and Affective Neuroscience*, *9*(4), 487–493. https://doi.org/10.1093/scan/nst009.

Zhang, W. N., Chang, S. H., Guo, L. Y., Zhang, K. L., & Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders*, *151*(2), 531–539. https://doi.org/10.1016/j.jad.2013.06.039.