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Neural changes in reward processing following approach-avoidance training for depression

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Abstract

Altered approach motivation is hypothesized to be critical for the maintenance of depression. Computer-administered approach-avoidance training programs to increase approach action tendencies toward positive stimuli produce beneficial outcomes. However, there have been few studies examining neural changes following approach-avoidance training. Participants with major depressive disorder were randomized to an approach-avoidance training (AAT) manipulation intended to increase approach tendencies for positive social cues ($n = 13$) or a control procedure ($n = 15$). We examined changes in neural activation (primary outcome) and connectivity patterns using Group Iterative Multiple Model Estimation during a social reward anticipation task (exploratory). A laboratory-based social affiliation task was also administered following the manipulation to measure affect during anticipation of real-world social activity. Individuals in the AAT group demonstrated increased activation in reward processing regions during social reward anticipation relative to the control group from pre- to post-training. Following training, connectivity patterns across reward regions were observed in the full sample and connectivity between the medial prefrontal cortex and caudate was associated with anticipatory positive affect before the social interaction. Preliminary evidence of differential connectivity patterns between the two groups also emerged. Results support models whereby modifying approach-oriented behavioral tendencies with computerized training lead to alterations in reward circuitry (NCT02330744).

Key words: depression; reward; neuroimaging; cognitive bias modification

Introduction

Depression is a common mental health disorder associated with significant functional disability (Pincus and Pettit, 2001; Kessler *et al.*, 2003; Dunlop *et al.*, 2005). Essential features of major depressive disorder (MDD) include loss of interest or pleasure, diminished energy and hopelessness (American Psychiatric Association, 2013). Together, these symptoms point to potential abnormalities in the approach system—a set of biobehavioral processes that motivate the individual to seek out positive, rewarding outcomes (American Psychiatric Association, 2013). Neural substrates linked to the approach system include the basal ganglia involved in reward signaling, orbitofrontal and medial prefrontal cortex (PFC) that modulates behavioral responses and decision-making, as well as a broader network involved in salience processing and action planning, including the amygdala, insula and anterior cingulate (Chau *et al.*, 2004; Knutson and Greer, 2008; Haber and Knutson, 2010). Individuals with MDD show deficits in approach motivation and reward sensitivity (Trew, 2011; Dillon *et al.*, 2014; Nusslock and Alloy, 2017); they are less likely to seek out rewarding experiences (Hopko and Mullane, 2008); are less behaviorally responsive to reward than are non-depressed individuals (Pizzagalli *et al.*, 2008) and display abnormal neural responsivity (Chau *et al.*, 2004; Pizzagalli *et al.*, 2009; Treadway and Zald, 2011), including attenuated activation in fronto-striatal circuits during reward processing (Pizzagalli *et al.*, 2009; Dillon *et al.*, 2014; Hoflich *et al.*, 2019). Identifying ways to directly modify basic mechanisms of impaired approach motivation and reward responsiveness in MDD may inform new or complementary treatment approaches.

Cognitive behavioral therapy is a first-line psychosocial treatment for MDD that incorporates exercises to modify thinking and/or behavioral patterns that may partially address approach system dysfunction (Cuijpers *et al.*, 2007, 2008; Mazzucchelli *et al.*, 2009; Ekers *et al.*, 2014). For example, behavioral activation exercises emphasize structured increases in overt behaviors that are likely to bring about reinforcing environmental contingencies (Hopko *et al.*, 2003). Several neuroimaging studies point to treatment-related changes supporting the malleability

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of approach system functioning (Dichter *et al.*, 2009, 2010; Mori *et al.*, 2017; Shiota *et al.*, 2017; Yokoyama *et al.*, 2018). However, existing interventions are not universally effective and outcomes regulated by the approach system (e.g. positive affect) appear difficult to change (Craske *et al.*, 2016; Dunn *et al.*, 2020). Given the predominance and impact of approach-related deficits in depression, exploring innovative ways of targeting the approach system may have clinical utility.

Computer-based paradigms that target approach-oriented behavioral tendencies are an alternative way to reduce clinical symptoms. Behavioral assessment of implicit approach-avoidance tendencies was developed based on evidence that positively evaluated stimuli typically automatically elicit motor approach behaviors, whereas negative stimuli trigger avoidance (Rinck and Becker, 2007). Standard approach-avoidance behavioral assessments display valenced stimuli and ask the participant to pull a joystick (arm flexion; approach) or push it away (arm extension; avoidance) with faster approach *vs* avoidance movements typically seen for positive stimuli (Cacioppo *et al.*, 1993; Taylor and Amir, 2012). Using this paradigm, maladaptive automatic approach-avoidance tendencies characterized by diminished approach of positive cues are apparent in anxiety and depression (Heuer *et al.*, 2007; Vrijsen *et al.*, 2013; Radke *et al.*, 2014a; Bartoszek and Winer, 2015; Fleurkens *et al.*, 2018; Struijs *et al.*, 2018; Loijen *et al.*, 2020). The paradigm can be adapted for training purposes by establishing a contingency between stimulus valence and required responses to encourage the repeated approach of positive cues (Amir *et al.*, 2013; Kakoschke *et al.*, 2017). There is evidence that AAT can manipulate automatic approach action tendencies of dysphoric individuals (Vrijsen *et al.*, 2018), with initial data suggesting potential clinical efficacy for reducing depression symptoms (Becker *et al.*, 2019). If effective, AAT training holds promise as a complementary approach to standard interventions that can be applied to enhance approach behavior.

Assessment of approach-avoidance tendencies during functional magnetic resonance imaging (fMRI) in participants with major depression points to deficits in reward circuitry during approach of positive social cues (Derntl *et al.*, 2011). A behavioral manipulation like the AAT that targets approach system functioning would thus be anticipated to exert its effects through key reward-related fronto-striatal regions. To date, information about neural mechanisms of AAT are limited to effects observed in relation to alcohol cues in individuals with alcohol use disorders (Wiers *et al.*, 2011, 2015). However, the question of how AAT training exerts its clinical influence in depression, and specifically how the approach system is engaged during training, remains unanswered.

The goal of this study was to use a single-session experimental AAT as an initial step toward understanding training-related changes in brain function during social reward processing in MDD. We utilized an AAT procedure designed to increase approach for positive social cues by requiring participants to repeatedly pull pictures of faces displaying positive expressions toward them using a joystick. As these procedures were intended to modify evaluative responses to positive social cues, anticipation of social reward was measured during fMRI before and after the AAT using a well-established measure of reward processing [Social Incentive Delay task (SID); Spreckelmeyer *et al.*, 2009]. Prior work suggests that individuals with MDD show hypoconnectivity within fronto-striatal regions, including less connectivity between the ventromedial PFC and striatal regions implicated in detecting and hedonic responding to rewards (Manelis *et al.*, 2016; Young *et al.*, 2016). Moreover, functional connectivity involving reward processing regions predicts real-world relationships between approach behaviors and positive affect, suggesting that it may provide a complementary source of clinically relevant information (Heller *et al.*, 2020). Thus, both neural activity and functional connectivity were explored in order to capitalize on the potential for connectivity data to better capture neural differences (Camara *et al.*, 2009). We assessed social approach functioning by administering a social affiliation task in the laboratory with a trained confederate following the AAT (Aron *et al.*, 1997; Taylor and Amir, 2012). In keeping with previous findings that neural hyporesponse to positively valenced social stimuli is observed in depression and is improved with treatment (Schaefer *et al.*, 2006), we hypothesized that AAT would enhance approach system functioning, indexed by greater responsivity of reward circuitry during social reward anticipation (medial PFC, striatum and amygdala). We conducted exploratory analyses to evaluate whether individuals in AAT *vs* the control group differed in terms of strength or number of connections in fronto-striatal regions following the experimental manipulation and whether connectivity was associated with behavioral indicators from the social interaction task (ClinicalTrials.gov: NCT02330744).

Methods

Participants

The sample consisted of 32 individuals who met diagnostic criteria for MDD according to the Mini International Neuropsychiatric Interview (MINI Version 7.0.0.0 (Sheehan, 2014)). Participants were recruited through clinical referrals as well as posted announcements in community and online settings (e.g. ResearchMatch.org). Participants were required to be between the ages of 18 and 55 and to score 10 or higher on the Patient Health Questionnaire-9 (Kroenke *et al.*, 2001). Exclusion criteria were used to ensure that participants could safely complete the study procedures and to minimize confounding interpretations of our results: (i) pharmacological treatments that could affect brain functioning; (ii) concurrent psychotherapy, or empirically supported treatments for anxiety or depression in the past 6 weeks; (iii) active suicidal ideation; (iv) history of major neurological disorder or moderate-to-severe traumatic brain injury; (v) moderate alcohol or marijuana use disorder (past year); mild substance use disorder (all other drugs in past year); (vi) bipolar I or psychotic disorders and (vii) characteristics that compromise MRI safety. Forty-two individuals were assessed and 32 were randomized at the scan visit. Sample size was determined using a power calculation (power > 0.80 for two-sided $P < 0.05$) for detecting a between-within analysis of variance interaction term with a large effect size range ($d = 1.2$–1.6), which was based on our earlier work using AAT, which found a large effect (Taylor *et al.*, 2013; $d = 1.58$, Taylor *et al.*, 2014) as well as earlier work that found large neural effects of brief cognitive bias modification treatments ranging from $d = 0.9$ to 1.3 (Britton *et al.*, 2015; Wiers *et al.*, 2015). Recruitment occurred from January 2015 to April 2017 and ended when the project target was met. The current data reflect the primary outcomes measured for the trial; additional secondary outcomes were measured as reported in the trial preregistration and will be reported elsewhere. The final sample included 28 individuals after attrition and quality control checks (described below and Figure 1 CONSORT diagram). The project was approved by the UCSD Human Research Protection Program.

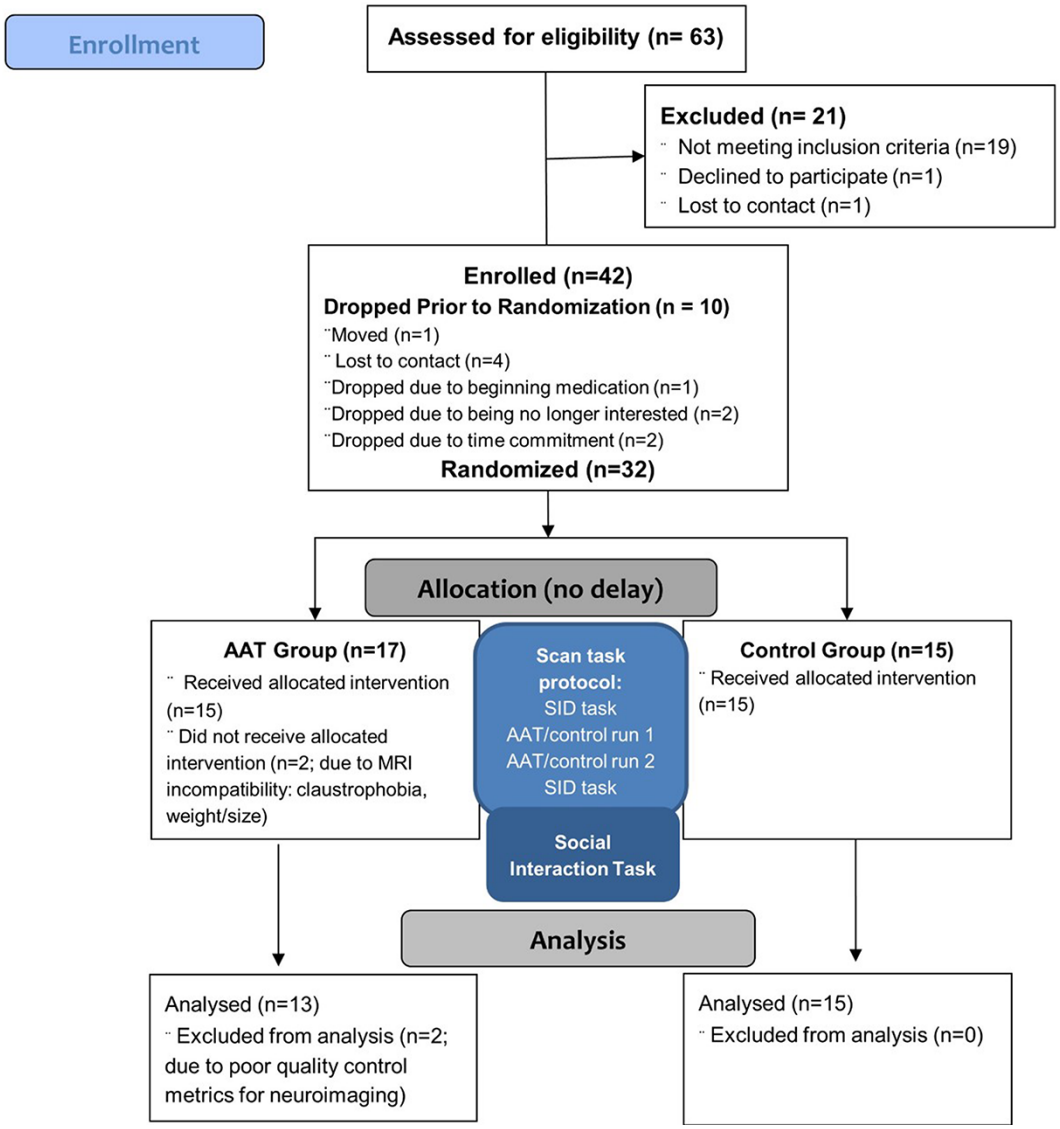

Fig. 1. CONSORT diagram.

Procedure

The primary aim was to evaluate the neural correlates of a single-session approach/avoidance training manipulation completed during MRI. Potential participants provided written informed consent and then completed a baseline eligibility session, followed by a session that included questionnaire measures, fMRI and out-of-scan social interaction task. The following questionnaire assessments were administered:

Depression severity

Participants completed the Beck Depression Inventory-II (BDI-II) (Beck *et al.*, 1996) to assess depression symptoms during the past 2 weeks.

Positive and negative affect

Participants completed the Positive and Negative Affect Schedule (PANAS; Watson *et al.*, 1988), a 20-item self-report measure of positive and negative affect over the past week.

Anhedonia

Participants completed the Mood and Symptom Anxiety Questionnaire (MASQ); the MASQ-Anhedonic Depression subscale [MASQ-AD (Clark and Watson, 1991)] was used to assess symptoms of anhedonia during the past week (e.g. 'felt like nothing was very enjoyable').

Anxiety

Participants completed the State Trait Anxiety Inventory-Trait [STAI-T (Spielberger *et al.*, 1983)] to measure general anxiety.

Experimental manipulation: fMRI approach/avoidance training. During fMRI, participants viewed face images (Tottenham *et al.*, 2009) on a computer screen and were instructed to move a joystick in response to the color of the border surrounding each image. Response instructions were linked to the border color, rather than the content of the images, which facilitates training. Face types included positive or neutral expressions (Ferrari *et al.*, 2018). The pull motion made the image 'zoom' (i.e. become larger) to give

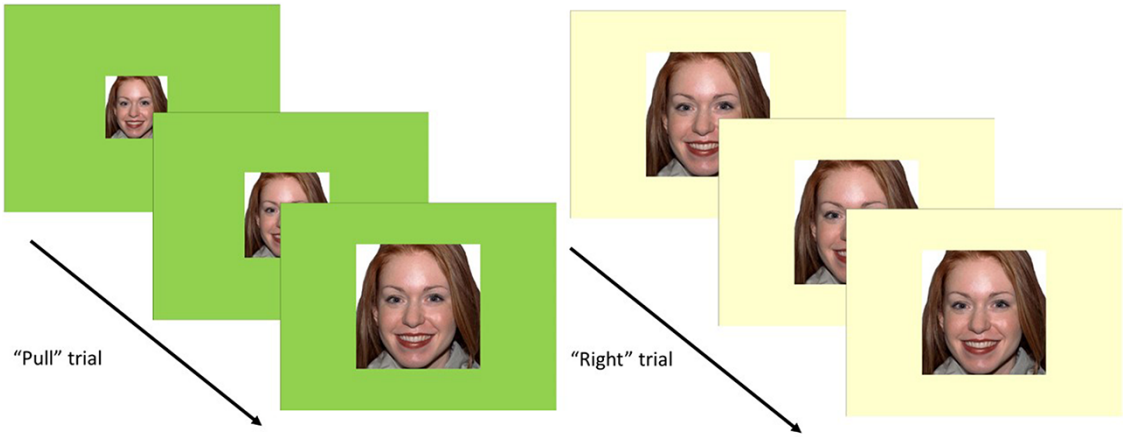

Fig. 2. Depiction of AAT task trials.

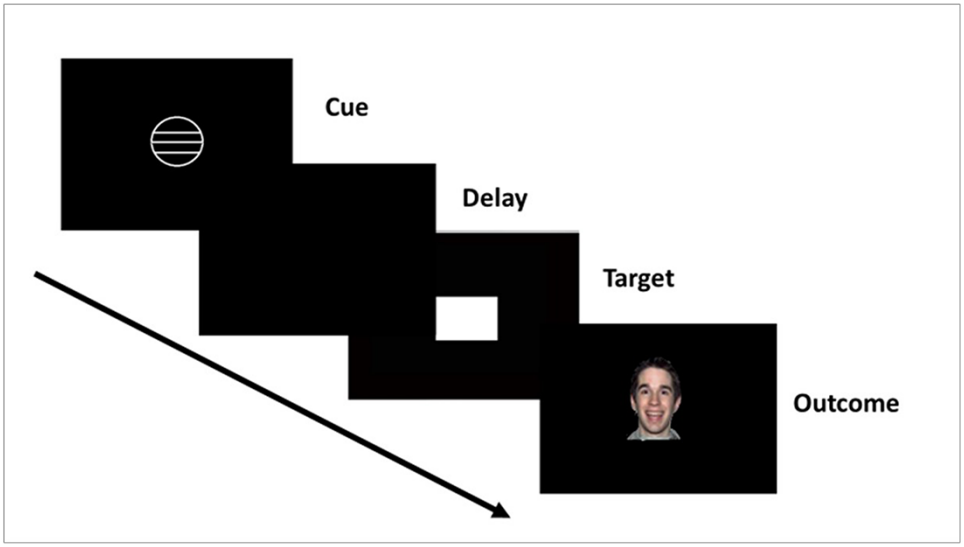

Fig. 3. Depiction of the SID task.

the appearance of approach. Participants moved the joystick to the right as a control motion (Taylor and Amir, 2012), which did not alter the size of the image (Figure 2). To experimentally manipulate automatic action tendencies, a contingency was set between positive facial expressions and approach behaviors in the active AAT condition but not in the control condition such that the majority of positive images (92%) were presented with a green border that indicated an instruction to pull, whereas the minority of neutral facial expression pictures (8%) were presented with a beige border and associated right movement instruction. In the control condition there was no contingency between instruction type and positive *vs* neutral pictures (i.e. 50% pull across both picture types). Prior to training, participants completed 12 practice trials that utilized different stimuli than those used during training. All participants saw four male and four female faces from the NimStim set displaying positive (happy) and neutral expressions during the training phase. During each training session, participants completed two runs of 96 trials per facial expression (~15 min). Participants were randomized (parallel group 1:1 allocation) to complete the AAT training or control (2 runs) using a computerized random number generation that created a condition code corresponding to either the AAT training or control condition. Approach bias was indexed by faster reaction times to approach *vs* move positive cues to the right on the AAT task. Experimenters and participants were blind to which condition number was assigned to AAT *vs* the control condition.

Social incentive delay task. Participants completed the SID (Spreckelmeyer *et al.*, 2009) to measure pre–post change in social reward anticipation across the AAT and control groups. In the task, participants were given the opportunity to either gain social reward or avoid social punishment (within separate trial blocks) following a successful reaction to a target symbol. Distinct cues preceding the target symbol indicated to the participant whether to anticipate a social reward, punishment or a neutral outcome. Low and high levels of reward or punishment were designated via one or three lines, respectively, inside the appropriate cue (Figure 3). Social reward and punishment were presented in the form of pictures of individuals with varying intensities of positive (smiling) and negative (angry) facial expressions, respectively. A blurred facial control stimulus served as the neutral cue. Participants gained low and high levels of social reward if their reaction to the target symbol was performed on time (i.e. hit response during the target display) and received the control stimulus if

they reacted too slowly (i.e. miss response after the target disappeared). Reward and punishment cues were presented in two separate blocks of 54 trials counterbalanced across participants; within each block, the order of cues was pseudo-randomized. Each trial began with a cue on the center of the screen (250 ms display), followed by a delay period (2250–2750 ms, jittered), and the target symbol (presented for 250 ms at the start of the task and individually adjusted thereafter depending on participant performance). The reward or neutral outcome was presented on the screen for 1650 and 300 ms after the target onset. The task difficulty was adjusted based on the participant's reaction time and approximate hit rate of 66%. Analyses focused specifically on change in responses to social reward anticipation in line with prior work and given the proposed mechanism of the AAT training procedures, i.e. inducing more positive valuations of target social cues (smiling faces).

Social interaction task. The social interaction task was an abbreviated version of a previously validated task designed to facilitate closeness between unacquainted partners (Aron *et al.*, 1997). The participant and a trained confederate alternated responses to a series of questions that gradually increased in the depth of self-disclosure they were designed to elicit (Taylor and Amir, 2012; Taylor *et al.*, 2017). Prior to the task, participants were informed that they would be getting to know an assistant who worked in the lab and, once the confederate was present, stated that the purpose of the task was to get to know one another by answering a series of questions about themselves (Aron *et al.*, 1997). Confederates were trained to deliver standardized responses to maintain consistency across participants and to act warmly toward participants using a scripted set of verbal and nonverbal behaviors. Participants completed the following questionnaires in relation to the interaction:

Positive affect

The PANAS-positive affect state scale was administered after instructions were provided about the upcoming social interaction task to provide a measure of anticipatory positive affect to a real-world opportunity for social reward.

Desire for future interaction

The Desire for Future Interaction scale [DFI (Coyne, 1976)] was administered to participants after completion of the task. The DFI has well-established reliability and validity (Voncken and Dijk, 2013). The DFI consists of eight items that assess the extent to which the rater would be willing to engage in a variety of social activities with their interaction partner in the future. The DFI was used as a measure of the participant's future approach motivation with respect to the social interaction task partner.

Analysis

fMRI acquisition and analysis

Participants were scanned in a 3T General Electric 750 scanner using an 8-channel head array coil. Each scanning session included a three-plane scout scan, a sagittally acquired spoiled gradient recalled sequence for acquiring T1-weighted images (172 slices; thickness: 1 mm; TI = 450 ms, repetition time (TR) = 8 ms, echo time (TE) = 3 ms; matrix: acquired 192X256; field of view (FOV) = 256 cm; flip angle = 12°; sagittal plane) and T2*-weighted axially acquired echo-planar imaging (EPI) scans to measure blood-oxygen-level-dependent (BOLD) signals (parameters: slice thickness = 3 mm; slice spacing = 1 mm; TR = 1.5 s, TE = 32 ms, flip angle = 80°; matrix = 64 × 64, FOV = 240 mm). The SID task was administered over two runs.

Single-subject analysis

Imaging analyses were conducted using Analysis of Functional Images. Standard preprocessing steps were used with the afni.proc.py tool including removal of outlying acquisitions, despiking, slice time correction, co-registration of anatomical and functional scans, spatial smoothing (6-mm half-maximum smoothing kernel) and warping to standardized MNI space. Visual inspection of quality and motion parameters was also conducted and identified two participants with excessive motion who were removed from analysis. Preprocessed time-series data for each individual were analyzed using a multiple regression model containing motion and task response regressors. Specifically, trials were coded on three levels (none, low and high), two type (reward and punishment) and two phase (anticipation and outcome) regressors. Regressors of no interest included motion parameters and the rating phase. Regressors shifted by a hemodynamic waveform (AFNI:waver), and individual preprocessed EPI data were entered into a general linear model.

Whole-brain analyses (primary outcome)

Whole-brain voxel-wise data were entered into a generalized linear model (3dLME) to evaluate regions of significant activation (Cox, 2016). The generalized linear test of interest compared activation across groups (AAT and control) over time (pre and post) to reward cues during anticipation (baseline *vs* any reward). Permutation testing within AFNI's 3dClustSim, which computes a three-parameter spatial autocorrelation function from the model residuals using 3dFHWMx to create an optimal smoothing kernel, were used to guard against identifying false-positive activations (voxel-wise a priori probability of 0.001 with corrected cluster-wise activation probability of 0.05). Significant activations with a minimum of 16 contiguous voxels were considered.

GIMME analysis (exploratory outcome)

Connectivity analysis was performed utilizing Group Iterative Multiple Model Estimation (GIMME), a package in R (https://www.nitrc.org/projects/gimme/) that models the directed functional connectivity of fMRI BOLD signal from predefined brain region of interest (ROI)s (Gates and Molenaar, 2012; Yang *et al.*, 2015). GIMME creates functional maps with sufficient model fit (2 or more fit indices) using a data-driven model building/pruning approach to estimate connectivity graphs and determine whether a specific ROI path improves model fit to time-series data, and estimates contemporaneous, lagged, and autoregressive paths among each time series. GIMME first creates a functional network map for the full sample, including group paths only if they are significant for a specified percentage of individuals (75%; Gates and Molenaar, 2012) to create a group-level map of contemporaneous and lagged directed connections that are common to most individuals. After defining the group map, unnecessary group-level paths are pruned and additional individual-level paths are implemented to improve model fit for each participant using Lagrange multiplier test equivalents. Then the common model is pruned by removing paths that are no longer acceptable. We utilized a confirmatory subgroup GIMME [CS-GIMME (Henry *et al.*, 2019)] analysis to explore potential group differences between individuals randomized to AAT *vs* control. CS-GIMME performs well at subgroup retrieval, even in small datasets (Gates *et al.*, 2017). Correlation matrices were created for each of the individual's

Table 1. Demographic and clinical characteristics

Patient demographic and clinical characteristics	AAT ($n = 13$)	Control ($n = 15$)	Test statistic, *P*-value
Gender (% female)	69%	60%	$\chi^2 = 0.26$, $P = 0.61$
Age, mean (s.d.)	25.69 (3.61)	28.60 (8.10)	$F(1, 26) = 0.89$, $P = 0.35$, $\eta 2 = 0.03$
Years of education, mean (s.d.)	15.61 (1.12)	15.86 (2.03)	$F(1, 26) = 0.16$, $P = 0.70$, $\eta 2 = 0.01$
Race (%)			$\chi^2 = 2.12$, $P = 0.83$
Caucasian	50%	33%	
Asian-American	8%	20%	
African-American	8%	7%	
Mixed race	25%	20%	
Other	8%	13%	
Unknown	0%	7%	
PANAS-PA, mean (s.d.)	19.84 (6.86)	19.86 (5.35)	$F(1,26) < .01$, $P = 0.99$, $\eta 2 < 0.01$
MASQ-AD, mean (s.d.)	84.23 (10.02)	82.73 (10.87)	$F(1, 26) = 0.14$, $P = 0.71$, $\eta 2 = 0.01$
BDI-II, mean (s.d.)	25.75 (10.66)	27.50 (6.59)	$F(1, 24) = 2.61$, $P = 0.61$, $\eta 2 = 0.01$
STAI-T, mean (s.d.)	45.38 (2.56)	46.53 (5.47)	$F(1, 26) = 0.48$, $P = 0.50$, $\eta 2 = 0.01$
PANAS—social anticipation	20.08 (8.77)	19.07 (4.00)	$F(1,26) = 0.15$, $P = 0.70$, $\eta 2 < 0.01$
DFI	40.23 (7.55)	41.79 (8.81)	$F(1,26) = 0.24$, $P = 0.63$, $\eta 2 = 0.01$
SID hit rate per trial type			
Pre—no reward	0.46 (0.17)	0.57 (0.11)	
Post—no reward	0.53 (0.15)	0.57 (0.07)	
Pre—reward	0.51 (0.12)	0.60 (0.06)	
Post—reward	0.56 (0.15)	0.62 (0.08)	
AAT bias score reaction time			
Run 1	43.38 (82.17)	33.83 (52.75)	
Run 2	81.88 (131.17)	11.13 (63.36)	

Table 2. Task-based whole-brain group × time interaction activations

ROI	Volume	x	y	z	T value, P	ROI	BA
1	123	11	61	18	3.92, 8.9e-5	Right medial frontal gyrus/anterior frontal pole	10
2	77	−1	29	53	3.97, 7.2e-5	Left dorsomedial frontal cortex	8
3	44	−40	−70	36	3.85, 1.2e-4	Left precuneus	39
4	29	−4	54	40	4.19, 2.8e-5	Left medial frontal gyrus	9
5	25	29	−71	−23	3.65, 2.6e-4	Cerebellum	19
6	22	10	25	8	3.76, 1.47e-4	Right caudate	
7	17	−6	−34	81	3.81, 1.4e-4	Left paracentral lobule	
8	16	42	5	−10	3.90, 9.6e-5	Right insula	13
9	24	−9	2	50	−4.04, 5.3e-5	Left cingulate gyrus	24
10	24	18	−41	61	−3.78, 1.6e-4	Right postcentral gyrus	3
11	20	−27	−53	49	−3.78, 1.6e-4	Left precuneus	7

Note: Center of mass coordinates in MNI coordinate space; voxel-wise a priori probability of 0.001 with corrected cluster-wise activation probability of 0.05.

post-training time series (preprocessed with motion and censor parameters regressed out) in the ROIs identified by the task-based group-level analysis. Consistent with earlier work using task-related designs (McCormick, 2014), we extracted measurement occasions when participants were engaged in anticipation of reward. We compared observed values for group-level paths across the AAT and control conditions and also examined potential differences in the number of subgroup-level paths within AAT *vs* control. We explored brain–behavior relationships by conducting Spearman rank order correlations between the paths identified in the sample and the self-report data from the social interaction task (positive emotion in anticipation of the interaction and desire to interact with one's partner in the future).

Results

Demographic and behavioral data

Table 1 presents the demographic and clinical characteristics of the sample. There were no statistically significant demographic or clinical differences (i.e. positive affect, depression, anxiety and anhedonia) between participants in conditions at baseline or after the manipulation (Table 1).

fMRI whole-brain effects

Voxel-wise whole-brain analysis of the interaction effect of time by group on anticipation of social reward revealed several statistically significant clusters spanning reward-related brain regions. Activation in the right medial frontal cortex extending into the anterior frontal pole, left medial and dorsomedial PFC (dmPFC), caudate, left precuneus, right insula, left paracentral lobule and cerebellum increased over time for those in AAT relative to control, while activation in the regions including the postcentral gyrus, precuneus and cingulate decreased (Table 2; Figures 4 and 5). Examination of the means suggested that at post-training, individuals in the AAT group showed significantly greater activation in the right medial frontal gyrus/anterior frontal pole, left medial frontal gyrus and right caudate, and lower activation in the cingulate gyrus relative to controls (see Supplemental Figure S1 for full results of between-group *t*-tests at pre- and post-timepoints, including effect sizes).

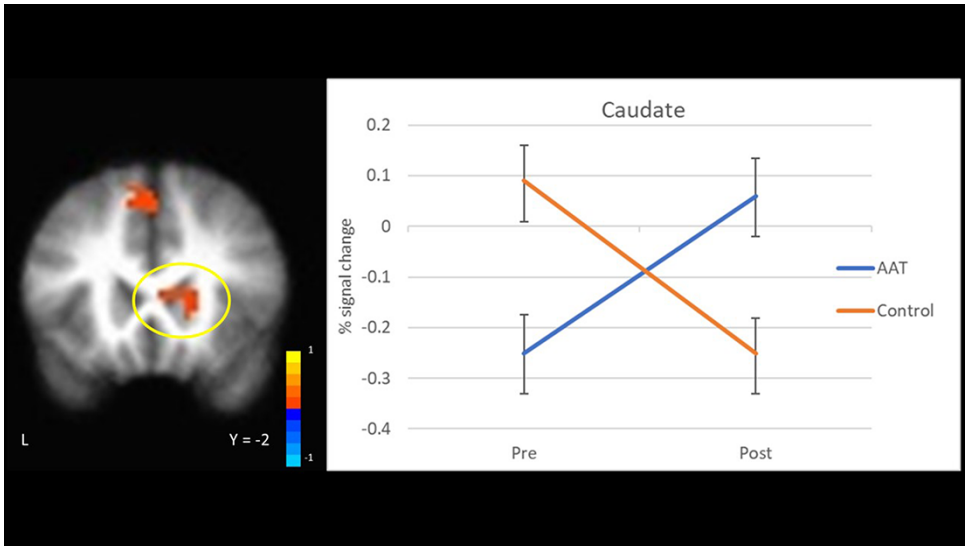

Fig. 4. Neural response during social reward anticipation to AAT *vs* control over time (group × time interaction) in the caudate.

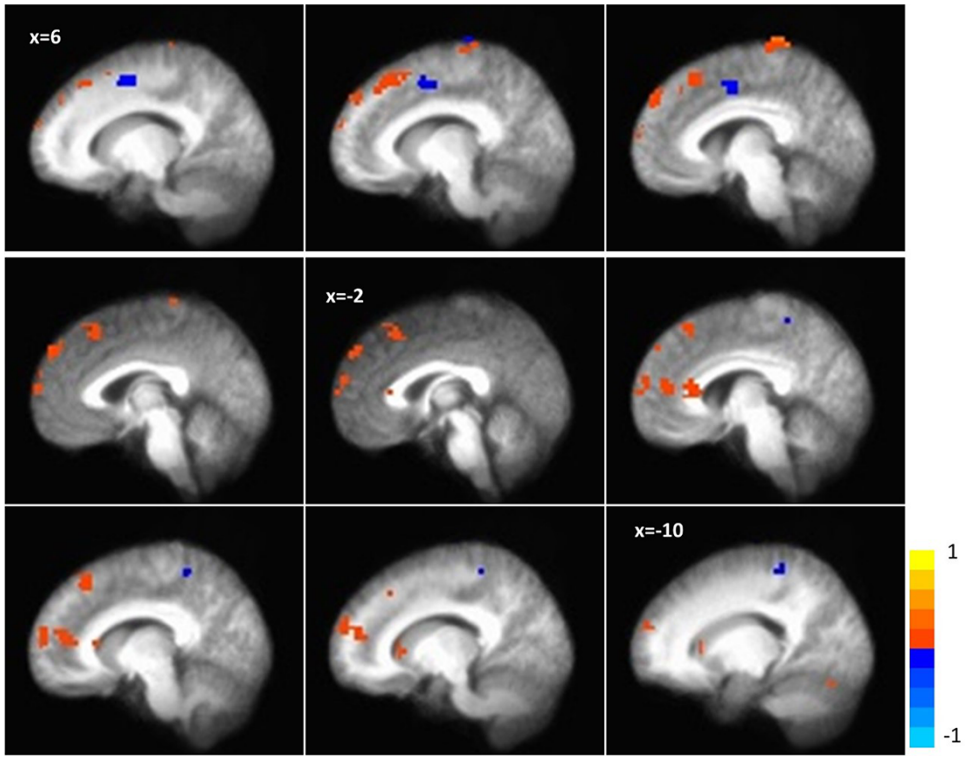

Fig. 5. Whole-brain activation during social reward anticipation (group × time interaction).

GIMME results

We first established the connectivity patterns that consistently reflected connections across ROIs during anticipation of social reward across both groups (Figure 5). Connections were observed between the right medial frontal gyrus/anterior frontal pole to the caudate and to the left medial frontal gyrus, as well as dmPFC to the precuneus and to the right medial frontal gyrus/anterior frontal pole (Table 5; Figure 6). Greater connectivity between right medial frontal gyrus/anterior frontal pole and caudate was significantly associated with higher PANAS-positive affect ratings in anticipation of the social interaction ($r^2 = 0.21$, $P = 0.02$) but no statistically significant relationship with the DFI score was observed (P values >0.1). We then examined group differences in the connectivity graphs for individuals in AAT and control groups to determine if there were differences in connectivity strength, number or patterns following AAT relative to the control condition. We did not observe any differences between the AAT and control groups in the strength of paths that were identified across participants (Table 3). Overall, the groups had a similar number of unique additional paths but different connectivity patterns. Individuals in the AAT condition demonstrated additional paths connecting the precuneus–postcentral

Table 3. Full group paths from GIMME connectivity analysis and between-group statistics

ROI (#)	M	s.d.	F-stat	P	η2
(1) Right medial frontal gyrus/anterior frontal pole—(6) right caudate	0.38	0.2	0.08	0.78	<0.01
(1) Right medial frontal gyrus/anterior frontal pole—(4) left medial frontal gyrus	0.36	0.24	0.21	0.65	0.01
(2) Left dorsomedial frontal cortex—(1) right medial frontal gyrus/anterior frontal pole	0.31	0.18	0.01	0.94	<0.001
(2) Left dorsomedial frontal cortex—(3) left precuneus	0.26	0.13	0.06	0.81	0.002
(1) Right medial frontal gyrus/anterior frontal pole (lag)—(1) right medial frontal gyrus/anterior frontal pole	0.6	0.15	0.21	0.65	0.01
(9) Left cingulate (lag)—(9) left cingulate	0.38	0.14	0.97	0.34	0.04
(11) Left precuneus (lag)—(11) left precuneus	0.46	0.16	0.09	0.76	<0.01
(3) Left precuneus (lag)—(3) left precuneus	0.6	0.17	0.39	0.54	0.02
(7) Left paracentral lobule (lag)—(7) left paracentral lobule	0.47	0.17	0.15	0.7	0.01
(4) Left medial frontal (lag)—(4) left medial frontal	0.56	0.16	0.2	0.66	0.01
(6) Right caudate (lag)—(6) right caudate	0.34	0.18	0.38	0.55	0.02
(5) Right cerebellum (lag)—(5) right cerebellum	0.49	0.16	1.39	0.25	0.06
(8) Right insula (lag)—(8) right insula	0.029	0.24	1.98	0.17	0.08
(10) Right postcentral (lag)—(10) right postcentral	0.48	0.19	0.03	0.87	0.001
(2) Left Dorsomedial frontal cortex (lag)—(2) left dorsomedial frontal cortex	0.59	0.16	1.25	0.27	0.05

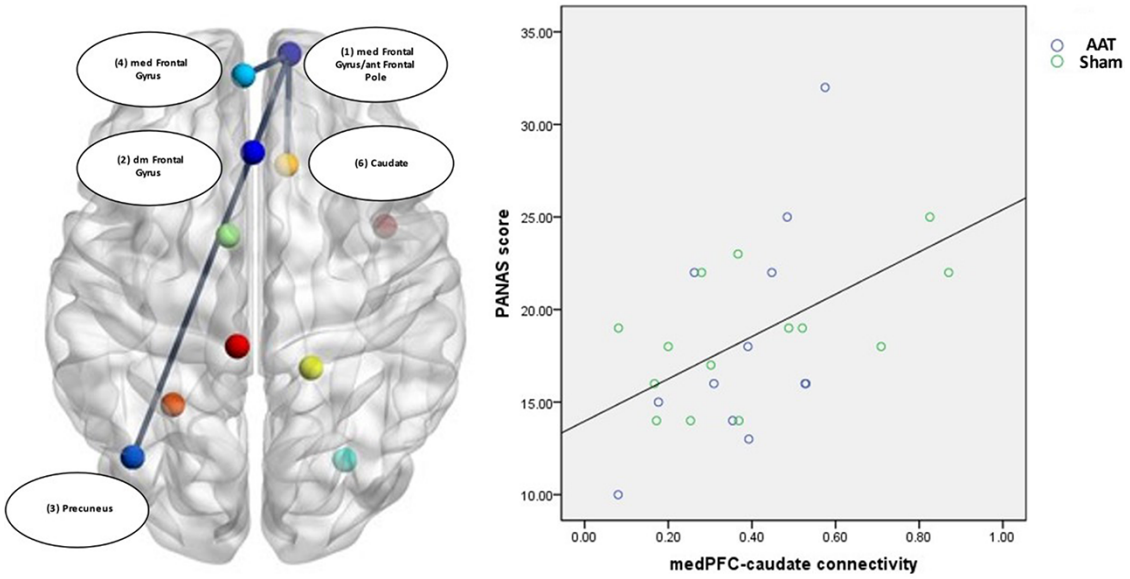

Fig. 6. ROI connectivity in the full sample.

gyrus, medial PFC–cerebellum and postcentral gyrus–cingulate (Figure 7A, Table 4). Individuals in the control condition showed additional paths between the cingulate–precuneus, cingulate–postcentral gyrus, right cerebellum–paracentral lobule and dmPFC–cerebellum (Figure 7B, Table 5).

Discussion

This study sought to examine neural mechanisms that might account for effects of computerized AAT on approach system functioning in individuals with MDD. Consistent with hypotheses, individuals in the AAT training condition showed increased activation in the striatum and medial PFC extending into the anterior frontal pole during social reward anticipation relative to those in the control condition. Additional reward-related regions (parietal cortex and insula) were also differentially activated by the training *vs* control. Irrespective of group assignment, neural activation during social reward anticipation was characterized by connectivity across these reward regions, with outward hubs from the right medial frontal gyrus/anterior frontal pole and dmPFC. The magnitude of connectivity between a region of the medial PFC extending into the anterior frontal pole and striatum was associated with self-reported positive affect during anticipation of the laboratory social interaction, suggesting that this path could be relevant to understanding real-world social responsivity. The AAT and control group each demonstrated additional unique group connections across ROIs, but a similar number of paths. Taken together, findings suggest that one potential effect of AAT may be enhanced engagement of reward-related circuitry in individuals with MDD and that distinct patterns of neural connectivity can be observed across AAT *vs* a control comparator.

Individuals with MDD demonstrate dysfunction of approach system functioning measured across biobehavioral domains, including blunted affective response to pleasant cues and rewards (Henriques and Davidson, 2000; Sloan and Sandt, 2010), implicit approach action tendencies (Wang *et al.*, 2006; Seidel *et al.*, 2010; Radke *et al.*, 2014b; Bartoszek and Winer, 2015), reward learning (Pizzagalli *et al.*, 2008) and neural responsivity

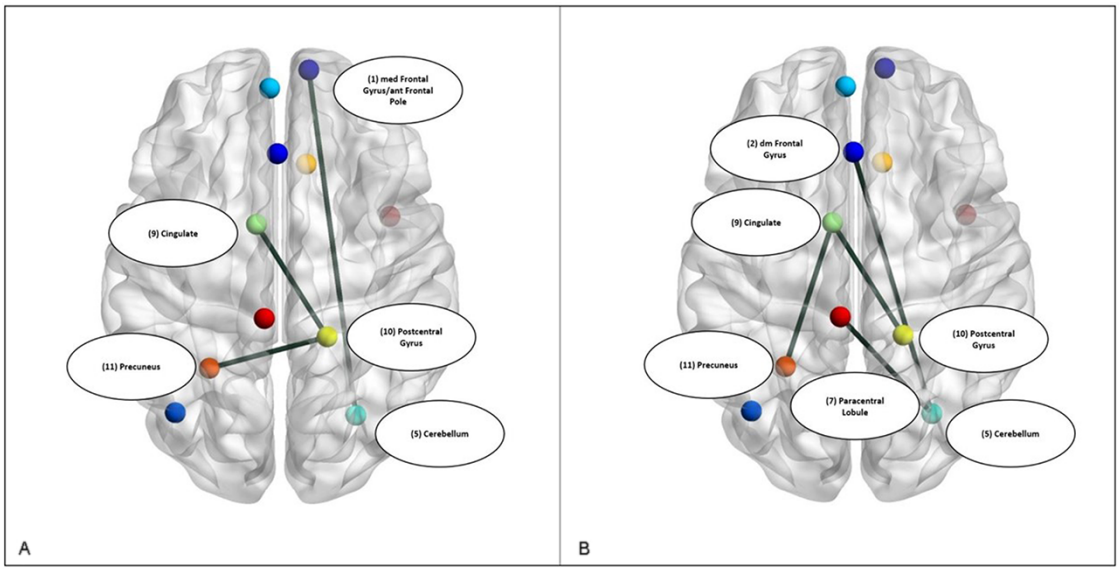

Fig. 7. ROI connectivity in the AAT (A) and control (B) subgroups.

Table 4. AAT group paths from GIMME connectivity analysis

ROI (#)	M	s.d.
(11) Left precuneus—(10) right postcentral gyrus	0.32	0.18
(1) Right medial frontal gyrus/anterior frontal pole—(5) cerebellum	0.30	0.23
(10) Right postcentral gyrus—(9) left cingulate gyrus	0.31	0.12

Table 5. Control group paths from GIMME connectivity analysis

ROI (#)	M	s.d.
(9) Left cingulate gyrus—(11) left precuneus	0.29	0.21
(9) Left cingulate gyrus—(10) right postcentral gyrus	0.21	0.24
(5) Cerebellum—(7) left paracentral lobule	0.23	0.20
(2) Left dorsomedial frontal cortex—(5) cerebellum	0.21	0.15

(Schaefer *et al.*, 2006; Derntl *et al.*, 2011; Treadway and Zald, 2011; Zhang *et al.*, 2013; Nusslock *et al.*, 2015). Approach-related neural systems include fronto-striatal circuitry implicated in pleasure and reward processing (Berridge *et al.*, 2009; Haber and Knutson, 2010; Kringelbach and Berridge, 2010), which operate via dopaminergic projections along mesolimbic and mesocortical signaling pathways connecting midbrain nuclei to the ventral striatum and to cortical regions (e.g. medial PFC, insular cortex and anterior cingulate cortex) (Treadway and Zald, 2011; Nusslock and Alloy, 2017). Observations of hyporesponsiveness in key reward processing regions during anticipation of reward (e.g. ventral striatum) (Forbes *et al.*, 2009; Smoski *et al.*, 2009; Admon and Pizzagalli, 2015; Arrondo *et al.*, 2015) and abnormalities in fronto-striatal connectivity (Furman *et al.*, 2011; Manelis *et al.*, 2016; Quevedo *et al.*, 2017) in individuals with MDD highlight this circuit as a potential neurobiological marker and treatment target.

Enhanced neural responsivity in fronto-striatal regions to social reward anticipation during the SID task for those in AAT *vs* control provides preliminary evidence of malleability of reward-related circuitry with repeated practice. Earlier work demonstrates that anticipation of reward is associated with the recruitment of striatal and PFC regions in healthy individuals (Ernst *et al.*, 2004; Liu *et al.*, 2011). We observed that individuals with depression who completed AAT showed increased activity in the caudate as compared to those completing control training. The caudate is considered to be a key hub for reward-related processing (Chau *et al.*, 2004; Haber and Knutson, 2010; Treadway and Zald, 2011; Pizzagalli, 2014) and may have particular importance for shaping goal-directed behavior based on expectancies (Grahn *et al.*, 2008). Increased activation was also observed in an anterior region of the frontal pole, a region thought to guide attention and behavior in line with internal goals (Orr *et al.*, 2015), evaluate relationships between external stimuli and the self (e.g. self-relatedness) (Phan *et al.*, 2004; Lemogne *et al.*, 2012) and make inferences about the knowledge and beliefs of others (cognitive theory of mind processes) (Abu-Akel and Shamay-Tsoory, 2011; De La Vega *et al.*, 2016). To the extent that hypoactivation reflects deficits in processing socially rewarding stimuli, changes following AAT may reflect amelioration of reward responsivity deficits. It may also reflect changes in social approach orientation potentially via changes in self-referential evaluation of positive social cues. We observed a relative decrease in activation in regions including the cingulate and a region of the precuneus incorporating the intraparietal sulcus following AAT as compared to the control. Both regions are implicated in adaptive responding to conflict and inhibitory functioning (Botvinick *et al.*, 2004; Osada *et al.*, 2019). It is possible that reduced activation in these regions reflects a shift in reward perceptions, such that the anticipation of receiving positive social feedback resulted in diminished response conflict following repeated AAT wherein positive faces were repeatedly paired with approach behavior.

The results of GIMME connectivity analysis suggest that AAT *vs* control training results in different patterns of correlation across reward-related regions and highlight the interconnectivity of fronto-striatal regions while anticipating social reward cues. In particular, the observed connectivity between the medial PFC/anterior frontal pole and caudate across both groups aligns with earlier work demonstrating that reward anticipation is associated with frontal-striatal connectivity (Mayer *et al.*, 2011; Cohen *et al.*, 2012). PFC–caudate activity alongside connections

bilaterally across medial PFC regions were noted for individuals irrespective of randomization, suggesting that these pathways are common during the anticipation condition of the SID task. We observed that greater communication between the medial PFC/anterior frontal pole and striatum when anticipating positive social rewards in the SID task was associated with more positive emotion when anticipating a real-world social interaction. Individuals with MDD have been shown to demonstrate hypoconnectivity between the medial PFC and striatum (Young *et al.*, 2016); our observed findings point to a potentially important role of this frontal-striatal connection in social approach outcomes in depression. This region of the medial PFC is a core node in the default mode network that plays a central role in self-referential thinking, while the caudate is a key component of salience detection. Connectivity in these regions during anticipation of social reward during the SID may point to a greater perceived self-relevance of impending positive social cues (e.g. the positive feedback is for them) or a perceived link between the social reward and their actions or characteristics that makes the cues more salient. Translating to the social interaction, individuals who are more inclined to anticipate and link positive social outcomes to themselves via self-referential processing may experience greater positive emotions prior to socializing. In supplemental exploratory analyses using group randomization data, GIMME analysis identified divergent patterns of communication between ROIs across the AAT and control groups. The control condition reflected patterns with central cingulate activation and cerebellar activation, while the AAT group was characterized by connectivity involving the postcentral gyrus and medial PFC to the cerebellum. These patterns may reflect greater integration of reward processing circuitry with motor responses in the AAT *vs* control group (e.g. facilitated responding to reward based on practiced action tendencies during the AAT). Future replication will be needed to clarify the role of differential connectivity in clinical outcomes.

Evidence suggests that existing treatments for depression might normalize approach system functioning (Dichter *et al.*, 2009); however, those treatments target evaluative processes explicitly in comparison to AAT programs. AAT programs intervene on a specific component of approach system functioning by requiring individuals to repeatedly implement approach behaviors in the context of positive social stimuli, thus changing valuation and approach tendencies. AAT has shown promise as a method for modifying approach behaviors in samples with psychopathology (Loijen *et al.*, 2020); yet to date, knowledge about neurobiological effects of AAT on approach systems and the relationships between these systems and outcomes has been limited. Our results offer initial evidence that completing AAT *vs* control paradigms exerts neural effects on a novel task assessing social reward anticipation. Behavioral modification used in the AAT program may elicit changes via modification of neural substrates involved in processing social reward; however, future work examining treatment-related change with AAT is needed to fully elucidate neural mechanisms in the context of clinical intervention.

These data have a number of caveats. The sample was small. Future replication will be necessary to have confidence in the robustness and replicability of observed effects. While incentive delay tasks have been shown to produce reliable activations in regions including the striatum (Wu *et al.*, 2014; Elliott *et al.*, 2020), the use of a small sample combined with the high variability in neuroimaging data leads to the potential for measurement error to influence findings, making replication critical. Moreover, a larger sample size would permit the examination of brain–behavior relationships within the training and control groups separately, as well as more nuanced analysis of effects within individuals with depression, who are likely to display heterogeneity in approach system functioning (e.g. anhedonic symptoms). The current study was designed to examine neural changes during a relatively brief experimental manipulation. Controlled single-session paradigms may be useful in early stages of intervention development to isolate neural circuits that are and are not engaged in the absence of clinical symptom change, but the data cannot definitely speak to what neural changes might be observed over the course of AAT administered as an intervention program. Results comparing groups on outcomes obtained in the context of the social interaction task immediately following the 1-session program did not show statistically significant differences, pointing to a potential need for longer administrations to shift emotional/motivational reactivity and symptoms. Social cues were used in the current version of the AAT and SID consistent with prior literature in depressed samples (Radke *et al.*, 2014a), and thus future research is needed to evaluate reward response to other types of stimuli. Parameters of the AAT training and control programs (i.e. using a control condition with 50/50 contingency, using visually enlarging images) were selected based on the prior literature to match what would typically be administered in the course of a clinical trial. However, using an active control wherein individuals only pull stimuli (both positive and neutral) may not be truly inert. For example, there is evidence in non-clinical samples that implicit approach training for neutral faces shifts the valence of that stimuli in a positive direction (Woud *et al.*, 2011), suggesting that approaching both positive and neutral faces—without trained avoidance—may provide clinical benefit. We observed in our data that in some brain regions changes occurred in both groups in opposite directions, suggesting that the control condition may have exerted a different but still impactful effect [see for example (Blackwell *et al.*, 2017; Tiggemann and Kemps, 2020) on the impact of control group selection in cognitive bias modification trials]. Despite these limitations, the current study points to potential neural targets underlying AAT in MDD. Taken together, these data reveal that AAT programs could operate via enhancing activity in or communication across reward-related circuitry, which may relate to clinical and behavioral outcomes. The current data suggest that AAT may be a viable method for restoring neural functioning in reward-related circuitry in individuals with depression.

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Conflict of interest

Dr M.P. is an advisor to Spring Care, Inc., a behavioral health startup, and he has received royalties for an article about methamphetamine in UpToDate. Dr C.T. declares that in the past 3 years he has been a paid consultant for Homewood Health and receives payment for editorial work for UpToDate. Dr M.S. has in the past 3 years been a paid consultant for Acadia Pharmaceuticals, Aptinyx, Bionomics, Genentech, GW Pharma, Janssen, Nobilis Therapeutics and Oxeia Biopharmaceuticals. J.B., A.S. and S.-H.C. declare no conflicts of interest. These data have not been previously published.

Supplementary data

Supplementary data are available at *SCAN* online.

Author contributions

C.T. designed the study and wrote the protocol. C.T., J.B. and S.-H.C. managed literature searches and statistical analyses. All authors contributed to and have approved the final manuscript.

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