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Research paper

Early changes in neural circuit function engaged by negative emotion and modified by behavioural intervention are associated with depression and problem-solving outcomes: A report from the ENGAGE randomized controlled trial

Andrea N Goldstein-Piekarski[a,b,1], Joseph Wielgosz[a,b,1], Lan Xiao[a], Patrick Stetz[a], Carlos G. Correa[a], Sarah E. Chang[a], Nan Lv[c], Lisa G. Rosas[a], Philip W. Lavori[a], Mark B. Snowden[d], Elizabeth M. Venditti[e], Janine M. Simmons[f2], Joshua M. Smyth[g], Trisha Suppes[a,h], Megan A. Lewis[i], Olusola Ajilore[c], Jun Ma[c,1], Leanne M. Williams[a,b,1,*]

[a] *Stanford University, Stanford, CA, United States*
[b] *Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC) Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, United States*
[c] *University of Illinois at Chicago, United States*
[d] *University of Washington, United States*
[e] *University of Pittsburgh, United States*
[f] *National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, United States*
[g] *Pennsylvania State University, United States*
[h] *Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, United States*
[i] *RTI International, United States*

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ABSTRACT

Background: Depression exerts a staggering toll that is worsened with co-occurring chronic conditions such as obesity. It is imperative to develop more effective interventions for depression and to identify objective and biological plausible neural mechanisms to understand intervention outcomes. The current study uses functional neuroimaging to determine whether a behavioural intervention changes the negative affect circuit and whether these changes relate to subsequent improvements in both symptom and problem-solving outcomes in depressed patients with co-occurring obesity.

Methods: This study ('ENGAGE') was a pre-planned element of the randomized controlled trial, 'RAINBOW' (ClinicalTrials.gov NCT02246413). 108 depressed patients with obesity were randomized to receive an integrated collaborative care intervention (I-CARE) or usual care. Participants underwent functional neuroimaging using an established facial emotion task at baseline and two months (coinciding with the first two months of intervention focused on problem-solving therapy ('PST')). Amygdala, insula and anterior cingulate cortex activation was extracted using pre-planned definitions and standardized methods. The primary health and behavioural outcomes were depression symptom severity and problem-solving ability respectively, assessed at baseline, the main 6-month outcome point and at 12-month follow up. Mediation analyses used an intent-to-treat approach.

Findings: PST, relative to usual care, reduced amygdala activation engaged by threat stimuli at two months. This reduction mediated subsequent improvements in depression severity in an intervention-dependent manner. PST did not change insula activation at two months but did temper the strength of the relationship between insula activation and improvements in problem-solving ability.

Interpretation: The negative affect circuit may be an important neural target and potential mediator of PST in patients with comorbid obesity.

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* Corresponding author at: Stanford University, Stanford, CA, United States
E-mail addresses: leawilliams@stanford.edu (A.N. Goldstein-Piekarski), leawilliams@stanford.edu (L.M. Williams).
[1] These authors contributed equally to this work.
[2] Since development of this manuscript Dr. Simons now serves as Chief of the Individual Behavioural Processes Branch the National Institute of Aging

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Research in context

Evidence before this study

Depression and obesity commonly co-occur, with limited and variable treatment effectiveness. Randomised controlled trials have been conducted but few further an experimental mechanistic understanding of how behavioural interventions may exert early impact via changes in neural circuit functions, particularly negative affect circuits. A search was conducted for eligible clinical and experimental medicine studies of behavioural interventions of depression/mood disorders or obesity/overweight using functional magnetic resonance imaging focused on negative emotion/negative affect targets using PubMed and Cochrane Central Register of Controlled Trials on July 3rd, 2020. The search was open to all publications that had been reported on prior to July 3rd, 2020 and did not include language restrictions. Of these, only three controlled intervention studies were identified, and none examined negative affective circuits as the putative neural targets of behavioural interventions depression and/or obesity. The neural targets selected for the current study were guided by our previous systematic review in which meta-analyses, reviews, and empirical findings reproduced in at least two well-powered studies were prioritised.

Added value of this study

This study is the first to utilise an experimental medicine approach with neural circuit targets to reveal the mechanisms underlying response to behavioural intervention in patients with depression comorbid with obesity. The findings suggest that the early phase of intervention, focused on problem-solving and behavioural activation engages the neural targets focused on the amygdala and the anterior insula. As hypothesised, change in amygdala activation after 2 months of intervention was associated with improvement in depressive symptoms at 6 months, while changes in insula activation after 2 months were associated with problem-solving outcomes at both 6 and 12 months.

Implications of all the available evidence

Previous research identified the amygdala and insula as two target regions associated with depression pathophysiology as well as treatment response. New evidence from this study indicates that amygdala and insula regions of the negative affect circuit may be promising mechanistic targets for optimizing the efficacy of behavioural interventions for depression in those who may be especially functionally impaired due to comorbid obesity. Modifying these neural targets may be relevant to both clinical and functional recovery of depression.

1. Introduction

Depression is highly prevalent, affecting more than 300 million people worldwide, and is now the leading cause of global disease burden [1]. Depression further causes crippling economic impact, with an estimated cost to the global economy of US $1 trillion per year in lost productivity [2]. Depression commonly co-occurs with obesity [2–4] and this comorbidity imposes especially high disease burden and difficulties with depression management [5–8]. Thus, there exists an urgent need for new approaches that alleviate depression in the context of comorbid obesity.

To address this need we drew on an emerging scientific literature which supports applying the science of behaviour change with an experimental medicine framework. This approach is focused on identifying objective and biologically plausible measures that may mediate change, to develop, optimise, and evaluate behavioural interventions [9,10]. Our intervention focus was on an integrated collaborative care intervention incorporating problem-solving therapy (PST) for depression with behavioural activation strategies (Integrated Coaching for Better Mood and Weight Intervention [I-CARE]). A recent randomised clinical trial known as RAINBOW (Research Aimed at Improving Both Mood and Weight) showed that I-CARE is effective at treating depression in adults with co-occurring obesity and depression [11,12]. RAINBOW was the parent trial for the present study and the present study was known as ENGAGE [13]. In ENGAGE we focused on neural circuit targets assayed by neuroimaging. The goal was to evaluate candidate neural circuit targets that may be modified by behavioural interventions such as I-CARE, and in turn may mediate clinical outcomes relevant to depression in the context of obesity. The targets for the ENGAGE trial were a pre-planned element of the design and analysis strategy and outcomes were a pre-planned element related to the parent RAINBOW trial [11,13]. We drew on current knowledge about the timescale of activity-dependent brain plasticity [14] to inform hypotheses about the timescale within which the intervention would initially modify neural circuit function and for which neural changes would lead to subsequent clinical outcomes.

The negative affect circuit offers promising neural targets for probing the potential mechanisms of behavioural interventions for depression in the context of obesity. In humans, the amygdala and insula, and their interaction with medial cortical regions such as the anterior cingulate cortex (ACC), are key components of the negative affect [15–18]. These regions are robustly engaged by negatively valenced stimuli, such as faces signalling threat or sadness when assayed using functional magnetic resonance imaging [19,20]. Dysfunction in these regions is a hallmark of depressive disorder, thought to reflect a heightened reactivity to negative emotion that accompanies the negative mood features of this disorder [17,18]. Greater dysfunction in these regions is also associated with higher body mass index and obesity [21,22].

Meta-analyses indicate that neuroimaging markers may have particular promise for predicting response to behavioural therapies for depression and highlight the need for more controls to advance a consistent understanding of mechanisms and mediators [23] In a randomized trial using functional neuroimaging and focusing on the negative affect circuit engaged by a facial emotion task identical to the one used in ENGAGE, a primary study by the senior author found that pre-treatment hyper-activation of the amygdala specifically predicted subsequent non-response to antidepressant pharmacotherapy in depression [24]. In a further trial with functional neuroimaging, in which patients were randomised to receive cognitive behavioural therapy versus an antidepressant [25], greater activation of the insula as well as the amygdala prior to intervention predicted more improvement of depressive symptoms after 12 weeks. In this trial the amygdala and insula of the negative affect circuit were engaged using a complementary facial emotion perception task. Meta-analysis implicates greater pre-treatment ACC activity in symptom improvement following both cognitive behavioral and pharmacological interventions across several tasks [26]. Such findings from intervention trials, and from the fundamental literature on the negative affect circuit, motivate our focus on the amygdala, insula and ACC as primary targets for probing the neural mediating mechanisms of response to the I-CARE behavioural intervention in the present ENGAGE trial. At the same time, because these prior studies were designed to compare active treatments they were necessarily limited by the lack of a usual

care control [24,25]. The need for deploying neuroimaging in controlled trial designs to identify potential mediators has been highlighted in relation to pharmacotherapy [27]. To address this need in relation to a behavioural intervention, we used a controlled randomised design, established by the parent RAINBOW trial, to investigate changes in neural targets that occur within the first two months of intervention, arguably capturing brain plasticity [14], and that may mediate subsequent clinical outcomes. Within the negative affect circuit activation of the amygdala, insula and ACC were our primary neural targets and functional connectivity between these regions were secondary targets. For our outcome measures we focused on both symptoms of depression as our clinical outcome and on problem-solving ability as our behavioural outcome relevant to functional recovery from depression and as the central behavioural focus of the intervention delivered [28].

In ENGAGE we investigated the hypothesis that activation of the amygdala, insula and ACC regions of the negative affect circuit are changed by the I-CARE intervention and that intervention-related neural changes occurring within the first two months would be associated with an improvement in both depressive symptom severity and in problem-solving ability [28].

2. Methods

2.1. Ethics

The Institutional Review Boards for the Stanford University (IRB 35,732 and 41,837) and the University of Illinois at Chicago (2015−1324) approved the study. All participants in the study provided written informed consent.

2.2. Study design and participants

2.2.1. Primary sample

Study participants of ENGAGE were a subsample of 108 participants that were invited to participate in additional neuroimaging assessments from RAINBOW, the parent randomised clinical trial, which enrolled 409 participants [11,12] (Fig. 1 for CONSORT chart). Participants were adults with depression and obesity who were randomly assigned to receive an integrated collaborative care intervention or usual care over 12 months who [1] had Patient Health Questionnaire (PHQ-9) scores of 10 or greater, [2] had body mass indices of 30 or greater ($\geq$ 27 for Asian adults), [3] aged $\geq$ 18 years, and [4] did not have alcohol or substance-use disorder or meet any other exclusion criteria (e.g., pregnancy, inability to communicate well in English, plans to relocate). Those with active Axis I disorder other than Major or Minor Depressive Disorder or Dysthymia, with the exception of comorbid anxiety disorders, were excluded. For ENGAGE participants, additional imaging exclusions included weight $\geq$ 350 pounds due to scanner constraints, MRI contraindications, traumatic brain injuries, presence of a tumour or other known structural brain abnormality. The sample size of at least 100 participants for the ENGAGE subsample was selected in order to detect medium effect sizes (Cohen's d 0.3−0.5) in predicting treatment outcomes assuming 80% completion rates. Demographic information for the ENGAGE sample split by intervention arm is presented in Table 1. Participants in the ENGAGE study were recruited from November 29, 2015 to October 25, 2016 within 4 medical centres of Sutter Health's Palo Alto Medical Foundation (PAMF, San Francisco, USA), and the date of the last participant assessed at 12-month follow-up was October 30, 2017.

ENGAGE participants were 68% (73/108) female and ranged from 22 to 78 years old (mean=52.0, SD=11.7), 75% (81/108) non-Hispanic white adults, and 72% (78/108) had at least an undergraduate degree. No differences in baseline characteristics were observed between those participants in the parent trial who did and did not enrol in ENGAGE (see Table S1). Of these participants, 86 completed fMRI at 2 months, and 102 and 96 completed outcome assessment at 6 months and 12 months, respectively.

For the ENGAGE trial design we expanded on the parent RAINBOW trial in two main ways. First, we added a 2-month time point to the ENGAGE trial design to specifically test the role of change in neural circuit targets at 2-months as a mediator of subsequent clinical outcomes. The ENGAGE subsample also completed functional magnetic resonance imaging (fMRI) sessions at baseline and 2 months after randomisation coinciding with initial 2-month intervention phase of the I-CARE program. Clinical outcomes were determined by the parent RAINBOW trial and were assessed at baseline and at 6 and 12 months after randomisation.

Detailed protocols for both the RAINBOW [12,13] and ENGAGE [12,13] clinical assessments have been pre-registered in published protocol papers (included in Supplemental methods). The trial is registered with ClinicalTrials.gov (NCT02246413). Materials and data from this study are available subject to the restrictions described in the Data Sharing statement.

2.2.2. Healthy reference sample

Data for healthy controls forming our standardization sample was acquired from 50 healthy individuals who underwent the same scanning protocol at Stanford (mean age = 32.48, SD, 11.95). Inclusion criteria included no significant history of any psychiatric disorder, 18−60 years, fluency and literacy in English. Exclusion criteria were current antidepressant medication and/or psychotherapy, moderate or greater alcohol or substance use disorder, history of brain injury with >10 min loss of consciousness and which could interfere with assessments, current episode of psychosis or mania, medical or neurological disorder that impact brain images, suicidal intent that represents imminent risk, or sensorimotor impediment to completing assessments. Demographic information for the healthy reference sample is presented in Table 1.

2.3. Randomisation and masking

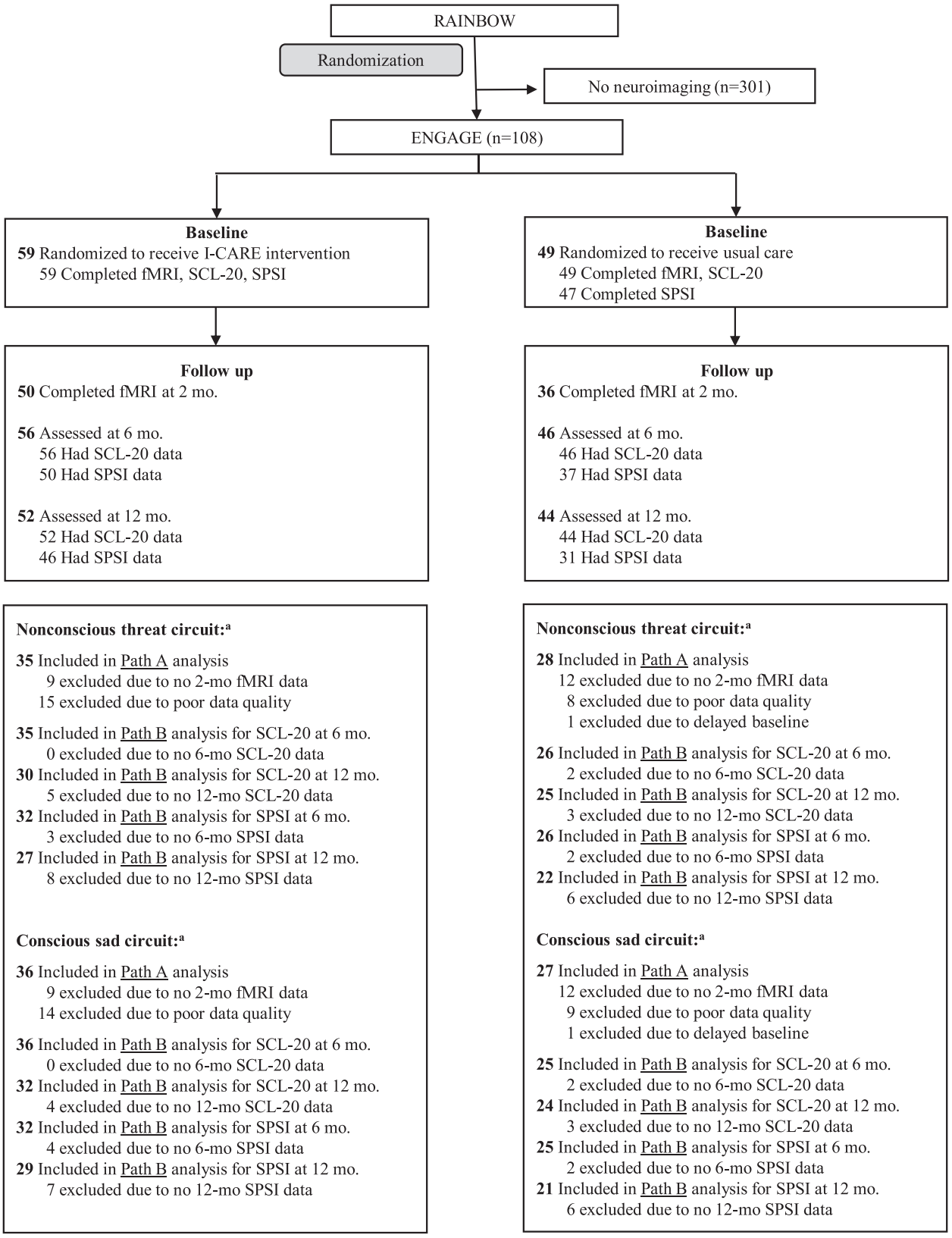
Participants were offered the option to enrol in RAINBOW only or in RAINBOW and ENGAGE during the informed consent. Enrolment was performed by trained study coordinators who were blinded to random assignments. Participants were assigned to receive usual care or the intervention by RAINBOW independent personnel using a validated automatic online randomization system which we published previously [29]. Investigators, outcome assessors, statisticians, neuroimaging team, and data and safety monitoring board members were blinded until after outcome data at 12 months were locked.

2.4. Procedures

Participants in both intervention and usual care groups received information on mental health services, weight management and wellness programs available at the medical foundation. Participants also received a wireless activity tracker with batteries, but no intervention materials such as worksheets or at-home educational videos. The intervention sessions and usual care were conducted at PAMF.

2.5. Intervention

The 12-month collaborative care intervention (I-CARE) is described in detail in Ma et al., 2019 [12]. In short, the integrated collaborative care intervention integrated the core components of two evidence-based behavioural interventions. The Program to Encourage Active, Rewarding Lives for Seniors (PEARLS) was a treatment with problem-solving as its core component and central theoretic basis as the first-line therapy, and was our focus in relation to depression and problem-solving outcomes [30,31]. PEARLS was supplemented with



Abbreviations: fMRI, functional magnetic resonance imaging; SCL-20, 20-item Depression Symptom Check List; SPSI, 25-item Social Problem-solving Index-Revised Short Form.

[a] Numbers excluded from Path A analyses are relative to participants at baseline; numbers excluded from Path B analyses are relative to participants included in Path A.

Fig. 1. CONSORT chart for participant inclusion in the primary sample.

Table 1
Baseline characteristics of primary sample for treatment groups, treatment groups combined, and healthy reference sample.

	PST[a] (*n* = 59)	Usual Care (*n* = 49)	Combined (*n* = 108)	Healthy (*n* = 50)
Age, mean (SD)	52.4 (11.6)	51.6 (12.0)	52.0 (11.7)	32.48 (11.95)
Sex, No. (%)				
Female	42 (71)	31 (63)	73 (68)	28 (56)
Male	17 (29)	18 (37)	35 (32)	22 (44)
Race/ethnicity, No. (%)				
Non-Hispanic White	46 (78)	35 (71)	81 (75)	27 (54)
Black	1 (2)	0 (0)	1 (1)	0 (0)
Asian/Pacific Islander	5 (8)	3 (6)	8 (7)	13(26)
Hispanic	4 (7)	7 (14)	11 (10)	8 (16)
Other or not reported	3 (5)	4 (8)	7 (6)	0 (0)
Education, No. (%)				
High school graduate or GED	2 (3)	4 (8)	6 (6)	4 (8)
Some college	10 (17)	14 (29)	24 (22)	3 (6)
Undergraduate degree	28 (47)	15 (31)	43 (40)	20 (40)
Graduate level work or degree	19 (32)	16 (33)	35 (32)	23 (46)
Body mass index, mean (SD)				
Both sexes	34.9 (5.2)	36.3 (4.9)	35.5 (5.1)	23.52 (3.32)
Women	35.2 (5.5)	37.6 (5.2)	36.2 (5.5)	22.89 (3.68)
Men	34.2 (4.2)	34.0 (3.5)	34.1 (3.8)	24.31 (2.66)
Weight, mean (SD), kg				
Both sexes	98.8 (17.1)	104.2 (13.2)	101.2 (15.6)	67.06 (12.42)
Women	94.7 (16.5)	100.8 (13.4)	97.3 (15.4)	60.63 (10.27)
Men	108.9 (14.5)	109.9 (11.0)	109.4 (12.6)	75.24 (9.95)
Height, mean (SD), cm				
Both sexes	168.1 (10.1)	169.8 (10.6)	168.8 (10.3)	168.48 (9.35)
Women	163.9 (8.4)	163.8 (7.2)	163.9 (7.8)	162.71 (6.44)
Men	178.4 (5.7)	180.0 (7.0)	179.2 (6.4)	175.83 (7.05)
20-item Depression Symptom Checklist score (SD)	1.5 (0.6)	1.6 (0.5)	1.5 (0.5)	-[b]
9-item Patient Health Questionnaire (SD)	14.0 (3.1)	13.4 (2.9)	13.7 (3.0)	0.84 (1.78)
7-Item Generalised Anxiety Disorder scale score (SD)	7.8 (4.3)	8.02 (5.0)	7.9 (4.6)	0.76 (1.17)
Taking antidepressant medications, No. (%)	24 (41)	19 (39)	43 (40)	0 (0)
Hospitalised during the last year, No. (%)	7 (12)	4 (8)N	11 (10)	0 (0)
Depression diagnosis or treatment, No. (%)	39 (66)	33 (67)	72 (67)	0 (0)
Employment status, No. (%)				
Full-time	34 (58)	28 (57)	62 (57)	26 (52)
Part-time	10 (17)	5 (10)	15 (14)	9 (18)
Unemployed	15 (25)	16 (33)	31 (29)	15 (30)
Income, No./total (%)				
<$75,000	8/53 (15)	15/46 (33)	23/99 (23)	20/49 (41)[c]
$75,000-$150,000	21/53 (40)	13/46 (28)	34/99 (34)	17/49 (35)[c]
>=150,000	24/53 (45)	18/46 (39)	42/99 (42)	12/49 (24)[c]
Insurance, No. (%)				
Preferred provider organization	42 (71)	27 (55)	69 (64)	-[b]
Health management organization	12 (20)	18 (37)	30 (28)	-[b]
Medicare fee for service	5 (8)	2 (4)	7 (6)	-[b]
Other Insurance	0 (0)	2 (4)	2 (2)	-[b]
Marital status, No. (%)				
Married or living with a partner	35 (59)	30 (61)	65 (60)	-[b]
Single, separated, divorced, or widowed	24 (41)	19 (39)	43 (40)	-[b]
Household size, No. (%)				
<2	14 (24)	7 (14)	21 (19)	-[b]
2	23 (39)	20 (41)	43 (40)	-
>=3	22 (37)	22 (45)	44 (41)	-[b]

[a] PST represents the initial 2-month intervention phase of the I-CARE program focused on a 7-step problem-solving therapy process.
[b] Data not collected in healthy control sample.
[c] Income categories for healthy controls were <$80,000, $80,000-$150,000, and $150,000+.

as-needed antidepressant medication. The Group Lifestyle Balance (GLB) program consisted of videos for self-study, grounded in social cognitive theory (for additional details related to the intervention delivery, see Supplemental materials) [32].

We focus specifically on the impact of the initial 2-month intervention phase of the I-CARE program on our neural circuit targets. This initial treatment phase included 6 in-person sessions for depression that implemented a 7-step problem-solving therapy as its core component, along with behavioural activation as a complementary component. For brevity this intervention is referred to hereafter as "problem-solving therapy" or "PST" for short.

2.5.1. Usual care

Participants in the intervention and usual care control continued to receive medical care from their primary care providers. These providers were notified of their patient's participation; however, they were not informed of his or her trial group assignment.

2.6. Procedures for acquiring and quantifying neural circuit mediator targets

Neural circuit targets were assayed using functional neuroimaging of the negative affect circuit of interest conducted at the Center for Neurobiological Imaging (CNI) at Stanford University. Neuroimaging was undertaken at baseline and at 2-month follow-up, immediately following the intensive phase of PST. Neural circuits targets were defined and quantified by the following pre-planned and established procedures:

2.6.1. (i) imaging sequences

We implemented previously established functional neuroimaging sequences and parameters as defined in our pre-specified protocol [13] (for details, Supplemental methods).

2.6.2. (ii) viewing of facial emotion task

The negative affect circuit of interest, with an *a priori* focus on the amygdala, insula and ACC, was engaged using an established viewing of facial emotion task. A standardised set of 3D evoked facial expressions of emotion stimuli were presented in pseudorandom order, with five repeated blocks of eight stimuli per block for each emotion relative to neutral blocks [33]. During the conscious viewing condition, each face was presented for 500 ms, with an interstimulus interval of 750 ms. We created a context for participants to continuously view the faces by instructing them that they would be asked post-scan questions about these faces. To elicit the negative affect circuit

in response to nonconscious threat stimuli, we presented the same fear and anger stimuli in a backward-masking design to prevent awareness. In this nonconscious condition, face stimuli were presented for 10 ms followed immediately by a neutral face mask stimulus for 150 ms, and with a stimulus onset asynchrony of 1250 ms to match that of the conscious condition [33]. Informed by findings for depression we focused on the nonconscious viewing condition for threat and the conscious viewing condition for sad.

2.6.3. (iii) pre-processing

Pre-processing and data analysis were performed using Statistical Parametric Mapping (SPM) software implemented in Matlab (SPM8; Wellcome Department of Cognitive Neurology) and the FSL [34] following previously established procedures [24,35]. Briefly, pre-processing of functional data included realignment and unwarping, normalization to a standardized template, and smoothing (for details, see Supplemental methods). Quality control diagnostics included removing scans with incidental findings, scanner artefacts, and signal dropout. Participants' data were included if no more than 25% (38/151) of time points were censored for frame-wise displacement or variance spikes. This resulted in total of $n = 89$ and $n = 74$ for the baseline and 2-month imaging sessions respectively.

2.6.4. (iv) defining neural circuit target regions of interest

Our regions of interest for the negative affect circuit engaged by threat and sad were defined in our protocol [13,18] and pre-planned analytic plan was established in a prior systematic procedure validated with the same facial emotion task as used in the present ENGAGE trial [36]. Primary target regions of interest were the subgenual ACC (sgACC) and amygdala (bilaterally) for threat and the pregenual ACC (pgACC), amygdala (bilaterally), and anterior insula (bilaterally) for sad. These regions were defined *a priori* and not derived using a discovery analysis with the present ENGAGE sample. Our *a priori* focus on these regions and pre-planned analytic strategy to test hypotheses, as outlined in the ENGAGE protocol [13] was informed by our synthesis of the imaging findings for depression [17,18] and prior trials in which imaging was included at the pre-trial baseline to predict outcomes for both behavioural and pharmacological interventions. We have established a systematic procedure for defining these *a priori* regions and for operationalizing them as anatomical masks for application in quantifying the activation within each region and the extent of connectivity between them [37]. Specifically, we first used Neurosynth to extract a spatial map of z-scores representing the negative affective network using search term "Threat." Peak z-scores in the Neurosynth mask were then identified using the Functional Neuroimaging (AFNI) 3dExtrema function. We operationalized masks as the anatomical boundary around these peaks. For the insula and ACC regions, given the larger spatial extent of these cortical regions, we imposed a restriction that each peak has a minimum z-score of 6 and each region extends no farther than 10 mm from the peak. For the amygdala, the Neurosynth map was intersected with anatomically defined boundaries from the Automated Anatomical Labelling (AAL) atlas [38]. Finally, these regions of interest masks were then intersected with each participant's grey matter mask to ensure specificity to the grey matter anatomy of each individual.

2.6.5. (v) quantifying neural circuit target regions of interest

Quantification of activation for the amygdala and insula target regions of interest followed our previously established systematic procedure and incorporated a healthy reference sample [36], as outlined in the following sections for both the healthy reference sample and the primary ENGAGE sample.

Activation for these target regions was first quantified for the healthy reference sample available to this study. We previously established that the healthy sample was characterised by good quality data [36]. Healthy reference values were computed for activation of regions for the contrast of each threat or sad minus neutral. A hemodynamic response convolved boxcar function was used to model the BOLD response for each block of emotional expressions to threat (fear and anger facial expressions) and to sadness relative to neutral face blocks. General linear models were then specified for each task to investigate the contrasts of interest. Frame-wise displacement and signal-variance spikes, plus the time point following, were included as nuisance regressors in each of the models.

Resulting activation values were mean-centred and scaled to be expressed as standard deviation units. For each individual participant in the primary sample, we then computed activation for the target regions, engaged by threat and sad, established using our a priori systematic procedures outlined in sections (iii) and (iv). We expressed the extent of dysfunction in these values in terms of standard deviation units referenced to the mean of the healthy reference sample. Through this procedure, activation values were interpretable relative to a healthy reference mean of zero. The activation of bilateral regions of interest were significantly and strongly correlated for the negative affect circuit evoked by Threat and Sad. These findings suggest a strong level of internal consistency between left and right-sided regions of interest at both baseline and 2-months follow up (see Table S2).

2.6.6. (vi) defining and quantifying additional regions within the negative affect neural circuit

Secondary analyses focused on functional connectivity with the subcortical regions of primary interest. Region-to-region connectivity for nonconscious threat was focused on connections between the amygdala and the sgACC. For sad, focused on connections between the amygdala and the pgACC as well as the insula and pgACC. Functional connectivity was computed using a psychophysiological interaction procedure (for details, Supplementary methods). Quantification of connectivity followed the previously established systematic procedure [36].

To provide an overall neural measure of negative affect circuit function we computed a global circuit score that combined activation and connectivity of constituent primary regions and the cortical regions to which they connect. This global score was an average of the standardized values for each constituent measure (for details, Supplementary methods).

2.7. Outcomes

The primary clinical outcome measure of depression severity and the primary behavioural outcome measure of problem-solving ability were acquired at baseline, the main 6-month outcome timepoint and again at 12-month follow-up at PAMF as outlined in both the ENGAGE and RAINBOW protocol papers [11,13]. Depression severity was measured using the average of the 20 items of the Depression Symptom Checklist (SCL-20). Each SCL-20 item had a range of 0 (best) to 4 (worst) [39]. Problem-solving ability was measured as the overall score from the self-administered Social Problem-Solving Index-Revised Short Form (SPSI-R:S) [40]. The SPSI total score is calculated as the average of positive problem orientation and rational problem-solving style, and the reversed scores of negative problem orientation, impulsivity/careless style, and avoidance style. The total score ranges from 0 to 20, with higher scores being indicative of better problem-solving abilities. Supplemental analyses examined these same measures acquired at 12-month follow-up. These primary outcome measures were reviewed centrally by the trial Data and Safety and Monitoring Board.

2.8. Statistics

Following our planned analysis strategy [13], we used the approach described by Kraemer at al. [41] to evaluate if early change

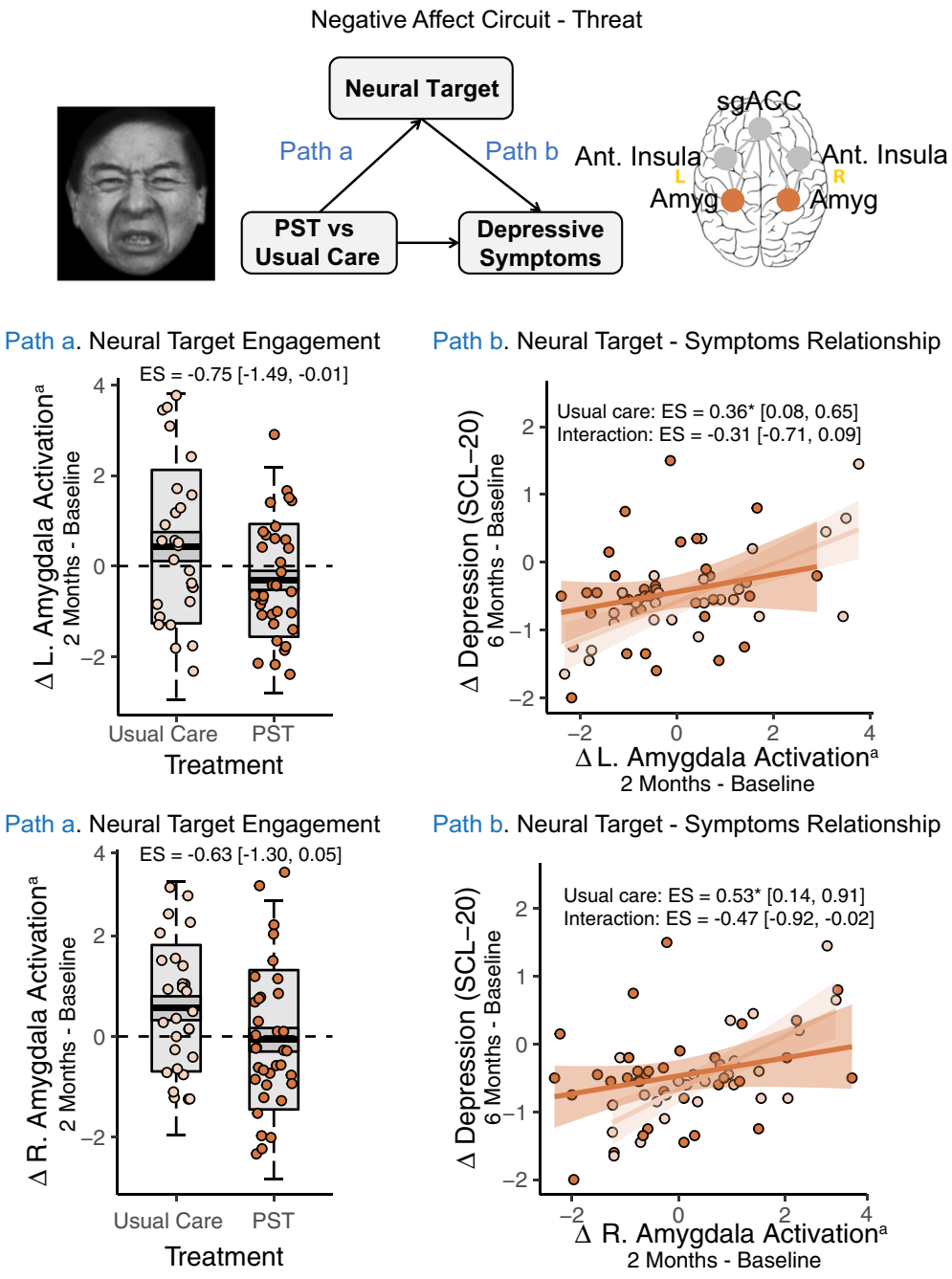


Fig. 2. PST-induced target engagement of amygdala engaged by nonconscious threat and subsequent depression symptom change at 6 months. Amygdala engagement by nonconscious threat stimuli at 2 months mediates subsequent depressive symptom improvements at 6 months. (Path a) Early change in bilateral amygdala engagement for PST versus usual care. (Path B) Association of early change in bilateral amygdala engagement with subsequent change in depression symptoms. All changes are relative to baseline session. For the box plots, the central thick black bar represents the mean, grey shaded boxes represent standard error (dark grey) and standard deviation (lighter grey) of the mean, and the whiskers represent 2 standard deviations of the mean. The impact on the intervention on clinical variables are reported in Ma et al. 2019 for the full RAINBOW trial and presented for the RAINBOW/ENGAGE sub-sample in supplement. [a]BOLD activation vs. neutral cue, z-scored. Abbreviations: ACC = Anterior Cingulate Cortex; sgACC = subgenual ACC; Ant Insula = Anterior Insula; Amyg = Amygdala; *R* = right; *L* = left; SCL-20 = Depression Symptom Checklist, 20-item; PST = initial 2-month intervention phase of the I-CARE program focused on a 7-step problem-solving therapy process.

in neural targets from baseline to 2 months mediates subsequent change in outcome from baseline to 6 months. A graphical representation of the mediation models tested are presented at the top of Figs. 2 and 3 for the negative affect circuit evoked by threat and sad respectively. This mediation approach was designed to address mediation within the context of a randomised controlled trial and requires that the change in the mediator occur during intervention and before assessment of outcomes [41]. In the case where a neural target significantly mediated treatment at 6 months, we examined whether the effect was sustained at 12 months. We first applied this mediation approach to analysis of our primary neural targets for both Threat (amygdala and sgACC) and Sad (amygdala, anterior insula, and pgACC). We then undertook secondary analyses to investigate whether observed effects are present for connectivity between these targets and cingulate regions and the global negative affect circuit. In our analyses and interpretation, we placed primary emphasis on estimation of effect sizes and confidence intervals. For all analyses, we calculated effect sizes and confidence intervals relative to the

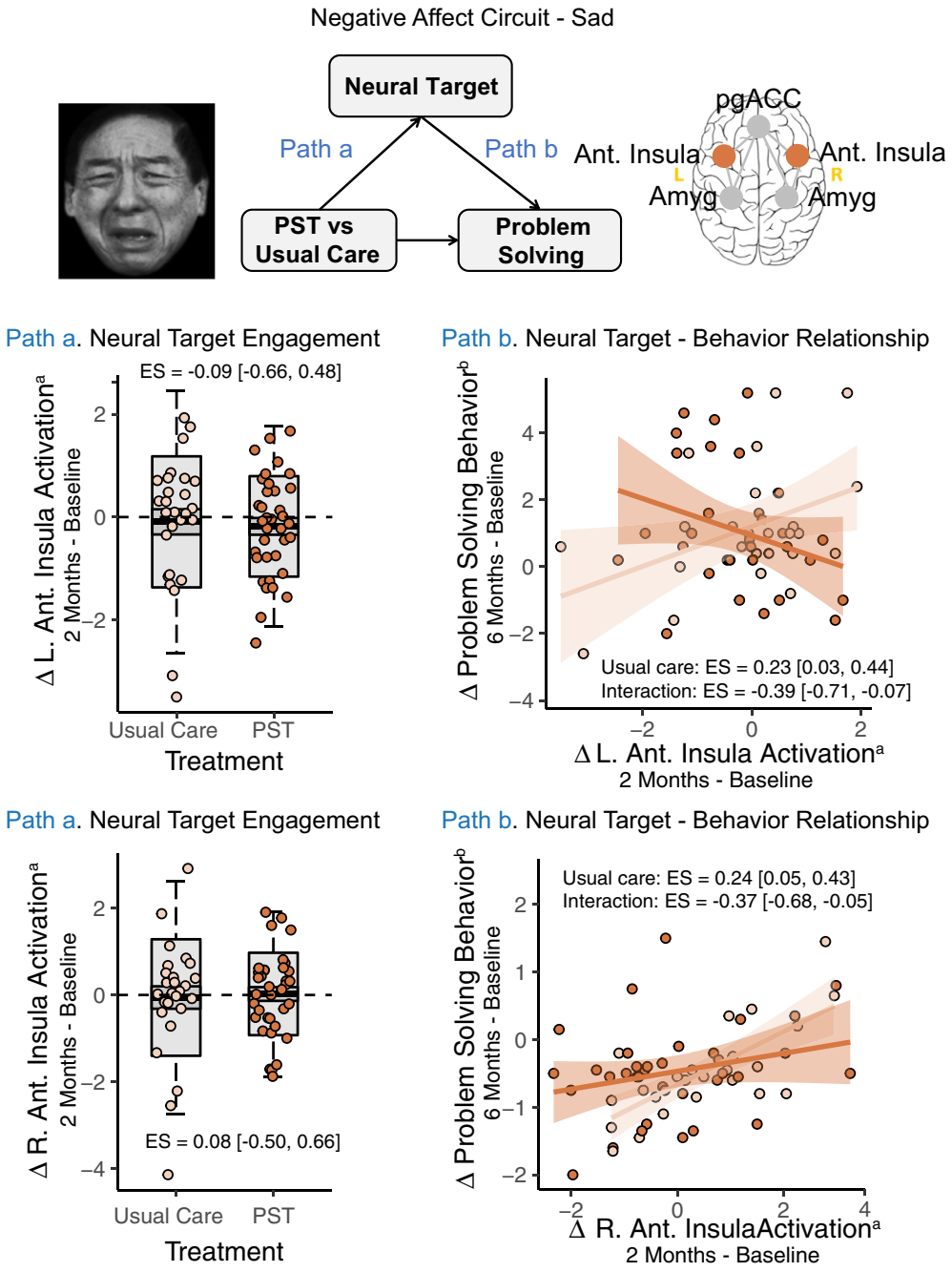


Fig. 3. PST-induced target engagement of anterior insula engaged by sad and subsequent problem-solving behaviour change at 6 months. Anterior insula engagement by conscious sad stimuli at 2 months is associated with subsequent change in problem-solving ability at 6 months (Path a) Early change in anterior insula engagement for PST versus usual care. (Path b) Association of early change in anterior insula engagement with subsequent change in problem-solving ability. All changes are relative to baseline session. For the box plots, the central thick black bar represents the mean, grey shaded boxes represent standard error (dark grey) and standard deviation (lighter grey) of the mean, and the whiskers represent 2 standard deviations of the mean. The impact on the intervention on clinical variables are reported in Ma et al. 2019 for the full RAINBOW trial and presented for the RAINBOW/ENGAGE sub-sample in supplement. [a]BOLD activation vs. neutral cue, z-scored; [b] Social Problem-Solving Inventory, Revised – Short form. Abbreviations: ACC = Anterior Cingulate Cortex; pgACC = pregenual ACC; Ant. Insula = Anterior Insula; Amyg = Amygdala; *R* = right; *L* = left; PST = initial 2-month intervention phase of the I-CARE program focused on a 7-step problem-solving therapy process.

standard deviation of the available pooled data from 1) the healthy reference sample (n = 50) described above for neural target measures and 2) all participants from the RAINBOW parent trial (n = 409) at baseline for outcome measures. Thus, effect size estimates indicates the magnitude of change in the outcome measures SCL-20 and SPSI-R:S associated with a change of one standard unit (referenced to one standard deviation in the healthy reference sample) in the circuit predictor. For all analyses we provide unadjusted p-values thresholded at an alpha level of 0.05. We provide p-values adjusted for false discovery rate (FDR) at a per-family threshold of Q = 0.10 (see Supplemental Methods and Tables S3-S8).

2.8.1. *Engagement of neural target (Path a)*

As seen in Figs. 2 and 3, for Path a we used independent t-tests to obtain differences between the intervention group and usual care for change in each potential mediator (amygdala/insula/ACC neural target) from baseline to 2 months. Specifically, the potential mediator

was entered as the dependent variable, and the treatment group as the independent variable.

2.8.2. Associated changes in neural target and intervention outcome (Path b)

For Path b, we used ordinary least square regression to assess the association of a potential mediator (amygdala/insula neural target) with an intervention outcome (i.e., SCL-20 and SPSI) in the usual care group and by interaction with the intervention compared with the usual care group, adjusting for the outcome at baseline. Participants were analysed based on the group to which they were randomly assigned and all available data we obtained.

2.8.3. Analysis of secondary neural targets and methodological checks

As a context for interpreting the analysis of primary neural circuit targets, we undertook analyses of specific additional neural targets that define the negative affective circuit engaged by threat and sad. For neural targets with behavioural associations as determined by mediation Path B, we also undertook analyses that served as methodological checks to aid in precise interpretation of our results for change in neural targets at 2 months. First, we examined the sustainability of observed early neural effects at the later follow up period. Second, to aid in interpretation of neural change in the ENGAGE participants we undertook a direct comparison of these participants with the healthy reference sample at baseline and at two months; at two months we separately compared PST and usual care groups with the healthy reference sample. This direct comparison allowed us to go beyond interpretation based on the standardized and norm-referenced neural circuit scores and provide a direct test, using independent-sample t-tests, of whether ENGAGE participants differed from healthy participants. Third, we examined whether antidepressant contributed to observed effects for neural target function at baseline and 2 months and fourth, we considered any potential effects of adverse events.

All analyses were performed on an intent-to-treat basis. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina).

2.9. Role of funders

No sponsor or funding source has a role in the design or conduct of the study; collection, management, analysis or interpretation of the data; or preparation, review or approval of the manuscript. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

3. Results

3.1. Primary neural targets

Amygdala activity evoked by threat was differentially impacted by PST and the resulting change in amygdala activity was associated with the change in clinical outcome of depression severity assessed by the SCL-20. PST produced an effect of blunting of the left amygdala engaged by threat stimuli at 2 months compared with usual care (ES=−0.75, 95% CI [−1.49, −0.01], Fig. 2 top panel Path a), although this effect was not significant at the adjusted alpha level (Table S4A).

Change in amygdala activity from baseline to 2 months mediated subsequent outcomes in SCL-20 symptom scores at 6 months. Specifically, in the absence of the PST (i.e., within the usual care group), a larger decrease in activation from baseline to 2 months in the amygdala was associated with greater reduction in depressive symptoms (right amygdala: ES=0.53, [0.14, 0.91], left amygdala: ES=0.36, [0.08, 0.65]; Fig. 2 Path B), significant at the adjusted alpha level (Table S5A). PST tempered this circuit-depression relationship within the right amygdala, such that the same degree of change in amygdala activity was associated with an effect of relatively smaller change in depressive symptoms for PST compared with usual care (Interaction ES=−0.47, [−0.92, −0.02]; Fig. 2 Path B), which was not significant at the adjusted alpha level (Table S5A). PST also showed a tempering effect on threat-related activation in subgenual ACC, such that the same degree of increase in activation was associated with an effect of relatively smaller impairment to problem-solving ability for PST compared with usual care (Interaction ES=-0.31 [-0.62, -0.01]), although this effect was not significant at the adjusted alpha level (Table S6A).

For primary neural targets evoked by sad we did not observe any significant effects for change from baseline to 2 months as a function of intervention group (Table S4A). However, while there was not an intervention effect on insula activity, change in insula activity evoked by sad, was associated with changes on the behavioural outcome of problem-solving ability. In the absence of PST (i.e., in the usual care group), a decrease in insula activation from baseline to 2 months was associated with larger impairments to problem-solving ability at 6 months (right insula ES=0.23 [0.04, 0.42]; left insula: ES=0.21 [0.01, 0.42], Fig. 3 Path B) which was significant for right insula but not for left insula at the adjusted alpha level (Table S6A). PST tempered and even abolished this circuit-problem-solving ability effect, such that the same degree of decrease insula activity was associated with a relatively smaller impairment in problem-solving ability compared with usual care (right insula: Interaction ES=-.33, [-0.64, -0.02]; left insula: Interaction ES=-0.35, [-0.66, -0.03]; Fig. 3 Path B) which was also a tendency at the adjusted alpha level (Table S6A).

3.2. Connectivity and global negative affect circuit targets

In secondary analyses, the effect of PST was also observed to generalize to the overall negative affect circuit evoked by threat (ES=−0.43 [−0.81, −0.06]), not significant at the adjusted alpha level (Table S4B). PST showed a tempering of the relationship between circuit function and problem-solving ability such that the same degree of increase in global circuit dysfunction was associated with an effect of relatively larger impairment to problem-solving ability for in the usual care group compared with PST (Interaction ES=0.57 [0.09, 1.06]), significant at the adjusted alpha level (Table S6B). Within the threat-evoked circuit, PST showed a similar effect for connectivity between subgenual ACC and amygdala, tempering relationship between connectivity in this pathway and problem-solving ability, such that the same degree of change in connectivity was associated with a relatively smaller change in problem-solving ability for PST compared with usual care (Interaction ES=-0.34 [-0.62, -0.06]; Table S6B)), significant at the adjusted alpha level. In the absence of PST (i.e., in the usual care group), a decrease in sad-evoked global circuit dysfunction from baseline to 2 months was associated with larger impairments to problem-solving ability at 6 months (ES=0.54 [0.04, 1.04]), though this was not significant at the corrected alpha level. PST showed a tempering effect on activation evoked by sad, such that the same degree of increase in global circuit dysfunction was associated with an effect of relatively smaller impairment to problem-solving ability for PST compared with usual care (Interaction ES=-0.78 [-1.45, -0.11]), significant at the adjusted alpha level (Table S6B).

3.3. Sustainability of neural effects at follow-up

Planned supplemental analyses were used to evaluate the sustainability of effects observed for change at 2 months In the absence of PST, decrease in left anterior insula activation was an effect that continued to show an association with reduced problem-solving ability at 12 months follow up (Usual care ES=0.23 [0.01, 0.46]), which was significant at the adjusted alpha level (Table S7A). This interaction was due to the effect of a decrease in insula activation remaining associated with relatively smaller impairments to problem-solving ability for the PST group relative to usual care (Interaction ES=-0.35

[-0.69, -0.01]) significant at the adjusted alpha level (Table S7A). Similarly, the effect of an association of reduced global circuit dysfunction with relatively smaller impairments to problem-solving ability for PST relative to usual care also remained apparent at 12 months (ES=-0.87 [-1.62, -0.12]), significant at the adjusted alpha level (Table S7B).

3.4. Comparison with healthy reference sample

At baseline, ENGAGE participants did not show a significant elevation in amygdala activity evoked by threat compared with the healthy reference sample, even though the direction of difference was consistent with an interpretation of unhealthy hyperactivation. At 2 months the PST group did not differ from the healthy reference sample on amygdala activation bilaterally. However, and consistent with a profile of persistent unhealthy hyperactivation in the absence of systematic intervention, the usual care group showed elevated activation of the bilateral amygdala at 2 months relative to the healthy reference sample (right amygdala: ES=0.56 [0.15, 0.98]; left amygdala: ES=0.49 [0.02, 0.96]), significant at the adjusted alpha level (Table S8A). No effects were observed between either treatment group and the healthy reference sample were observed for anterior insula (Table S8A) or with connectivity with the amygdala or the global negative affect score at 2 months (Table S8B).

3.5. Consideration of antidepressant use and adverse events

We did not observe any differences in neural circuit function at either baseline or at 2 months follow-up as a function of antidepressant use (Tables S9A-B).

Over the full duration of the study, there were two serious adverse events (i.e., fractures from falls while engaging in physical activity) and 37 non-serious adverse events (e.g., minor musculoskeletal injuries) that were possibly related to the study. These were randomly distributed across PST and usual care groups.

4. Discussion

In this study using functional neuroimaging to investigate neural mechanisms involved in the effect of a behavioural intervention incorporating PST, we found that PST induced early changes in neural circuit function that was associated with subsequent change in both depression and problem-solving ability outcomes. To our knowledge, this is the first intervention study utilising an experimental medicine framework to shed light on early neural changes that may explain why some individuals with depression improve in response to behavioural PST interventions relative to usual care, whether the response is sustained, and why others may not.

The PST was delivered as a core component of an integrated collaborative care intervention for patients with comorbid depression and obesity, randomly assigned to receive PST or usual care. Our first insight was that early changes within the negative affect circuit engaged by threat, and amygdala engagement in particular, mediated [41] subsequent improvements in depressive symptom severity and problem-solving ability. Early changes in circuit function were observed at two months after PST commenced. Early changes in both circuit engagement and in the strength of coupling between circuit change and symptom change differed between PST and usual care groups. Circuit function worsened for the usual care group, reflected in exacerbation of amygdala hyperactivation, and showed a stronger association with more severe depression outcomes. By contrast, both of these effects were tempered in the PST group. This suggests that compared with usual care, PST lessened amygdala activity in response to threat cues and lessened the exacerbation in depressive symptomology and maladaptive problem-solving behaviour for the same degree of amygdala hyperactivation.

These changes were observed when we probed the negative affect circuit using threat-related stimuli. Our second insight was that additional early changes in activation of the insula, observed when engaged by sad stimuli, were associated with later changes in problem-solving ability at 6 months and sustained this association at 12 months for the usual care group, accompanied by tempering of this relationship in the PST group. This suggests that targeted intervention strategies that can improve insula activity in response to sad cues may optimize the effect of PST on problem-solving ability.

Few studies to date have utilized biological markers in the context of randomized trials of behavioural therapies for depression [23]. However, a recent systematic review and meta-analysis found that, of these studies, neuroimaging shows promise in predicting response to behavioural therapies when compared to other biological markers such as inflammatory and immune function markers [23]. In a prior practical trial by one of our senior authors using the same emotion stimuli to engage the negative affect circuit, individuals with depression who failed to respond clinically to commonly prescribed antidepressants were characterised by heightened amygdala activity at the pre-treatment baseline compared with responders [24]. In this prior trial, clinical response was assessed within an acute period of 8 weeks. The present findings suggest that PST acted to prevent exacerbation of amygdala hyperactivation within the initial 2-month period of intervention which may in turn have protected against subsequent severity of depression symptoms, our primary clinical outcome, after a longer period of 6 months. Notably, the present study demonstrated a greater relative reduction in amygdala activity following PST over 2 months in the intervention group compared with usual care.

The inclusion of a behavioural outcome, problem-solving ability, in addition to the clinical outcome, depression symptom severity, was an additional novel feature of the present study. Within the negative affect circuit, insula activity engaged by sad (rather than threat-related) stimuli was furthermore distinctly associated with subsequent problem-solving ability outcomes. These early changes in insula activity engaged by sad and associated with changes in problem-solving ability were sustained through to 12-month follow-up. That changes in insula activity predict later problem-solving outcomes suggests a specific neural region of negative affect circuit function involved in depression-related processes targeted by PST. These findings inform the potential for targeted intervention strategies to modify this insula target and behavioural outcomes in a manner that is synergistic with the effect of PST on the amygdala and clinical outcomes. The association of anterior insula activity with changes in problem-solving ability also has implications for treating depression in the context of obesity. The anterior insula receives integrated homeostatic and interoceptive signals from visceral organs and is strongly implicated in conscious perception of emotional and autonomic states [42]. Not surprisingly, therefore, the insula has been identified as a key region involved in both depressogenic as well as obesogenic behaviours [43].

In light of our findings that the level of amygdala activity in response to negative affective stimuli was lessened (i.e., improved) in PST relative to usual care, that these changes occurred soon after the intensive initial phase of PST, and that they mediated later changes in clinical outcomes, it is clear that future research is needed to further probe the specificity of neural targets, intervention effects and the more granular time course of circuit-outcome changes.

This study is, to our knowledge, unique in assessing neural targets in relation to PST for depression in the context of comorbid obesity. Thus, the questions of whether the findings are specific to this highly vulnerable population, as well as refinements to the precision of our effect size estimates, some of which are smaller might have been anticipated based on prior literature, will require further investigation. In the parent RAINBOW trial, the range of response differed markedly [44] as is also the case for pharmacotherapy trials, indicating that a more stratified, personalized approach focused on

subgroups could be of value. In the parent RAINBOW trial, the range of response differed markedly [41] as is also the case for pharmacotherapy trials, indicating that a more stratified, personalized approach focused on subgroups could be of value. In particular, subsequent studies could pursue strategies based on augmentation of treatment or stratification based on the neural targets identified here, as well as the use of moderated mediation statistical designs, both to provide additional mechanistic insight and to further investigate the potential of treatment tailoring within a precision medicine framework. Although direct investigation of neural targets related to obesity was outside the scope of the present study, future studies are also warranted to explore potential targets for intervention that centre on the insula within the negative affect circuit, and problem-solving ability in weight as well as in depression management, as well as to identify relationships between neural and behavioural mediators of treatment response [45]. Future research is also warranted to extend the approach presented here to those additional neural circuits and potential target mediators supported as candidates by the accumulating basic neuroscientific literature on depression and obesity.

5. Caveats and limitations

The study has several limitations. First, allocation of participants from RAINBOW parent trial to the ENGAGE subsample occurred independently prior to treatment assignment, because of this link with the parent trial. This procedure might limit the net benefit of the random assignment based on Pocock's covariate-adaptive minimization for the present intervention study. Second, the participants in the ENGAGE sample were primarily non-Hispanic White, women, and college educated, and our healthy comparison sample was younger on average than the study group. Therefore, it will be important to determine whether the effects in the current study generalise to a more diverse sample. Relatedly, while treatment arms were matched in age, our healthy comparison sample was younger on average than the study group and thus we cannot rule out a contribution of age in comparisons between clinical participants and healthy controls. Future studies will be needed to assess whether the findings are replicable, in regard to the generalizability of the findings and the reproducibility of the design, measures and findings. In parallel, it would be important in further prospective designs to confirm that optimizing interventions to engage circuit target mediators positively impacts outcomes and to identify how those neural target mediators might be used in biomarker and stratification designs to optimise inventions for each person. Task-based neuroimaging measures have shown varying levels of within-subject reliability, and additionally, given higher levels of scanner bed movement in this population, we applied some leniency in our spike thresholding; both of these factors could have impacted our ability to detect changes in some targets. A further consideration is that the primary outcome measures were not available at the time of the 2-month imaging assessment because the 2-month time point was included specifically for ENGAGE and the outcome timepoints were pre-planned for the parent RAINBOW trial. While this was a planned aspect of the design, it limits the ability to resolve the precise time scale in which clinical and behavioural outcomes are changing as a function of intervention relative to changes in neural targets. As such, we cannot rule out the alternative that change in depressive symptoms preceded amygdala activation change. Finally, it would be important for our a priori negative affect circuit targets to be evaluated in future trials designed specifically to evaluate the extent to which they are reproducible and generalizable.

6. Conclusion

In summary, our findings identify neural circuit targets that are both changed by a problem-solving intervention for depression and relate to subsequent clinical and behavioural outcomes, and thus offer an important stepping-stone toward optimizing such interventions. First, we demonstrated that neural targets have promise for revealing potential mechanisms by which behavioural intervention mediates its effect on subsequent clinical outcomes. Second, our observation that PST produced early change in regions of the negative affect circuit which were associated with subsequent clinical outcomes suggests that PST may exert its impact on both depression and problem-solving ability through mechanisms that include early changes in stimulus-dependent brain plasticity. The neural mechanisms by which PST exerts its effect are not yet understood. Our findings made a step toward this understanding. They inform future trials in which elucidation of such neural mechanisms will be critical to optimizing delivery and implementation of interventions in clinical practice, in order to curtail the adverse consequences associated with complex presentations of depression.

7. Contributors

AGP, JW, LX, LMW and JM had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LMW, JM, LGR and PWL conceived and designed the study. SC acquired the imaging data and MBS and EMV with JM oversaw the design and implementation of the intervention. PWL and TS provided expertise in trial data analysis and psychiatry. CC and PS established the imaging management systems, LMW conceptualised the circuit score approach and AGP prototyped and implemented the scripts for the circuit quantification. NL coordinated the clinical data and operations for the study. AJP, JW and LX undertook the statistical analyses. AJP and JW interpreted the data and wrote the first draft of the manuscript. All authors contributed important intellectual content to the subsequent revisions and interpretation. All authors read and met the ICMJE criteria for authorship and agree with the results and conclusions of this Article.

Declaration of Competing Interest

LMW is on the Scientific Advisory Board for One Mind Psyberguide and the External Advisory Board for the Laureate Institute for Brain Research. JM is a paid scientific consultant for Health Mentor, Inc. (San Jose, CA). OA is the co-founder of Keywise AI and the servers on the advisory boards of Blueprint Health and Embodied Labs. TS reports in the last 36 months grants from Merck, grants from National Institute on Drug Abuse, grants from National Institute of Health, grants from Palo Alto Health Sciences, grants from Stanley Medical Research Institute, grants from Pathways Genomics, personal fees from Sunovion Pharmaceuticals, Inc., personal fees from American Society of Clinical Psychopharmacology, personal fees from Impel NeuroPharma Inc., personal fees from Intracellular Therapies, personal fees from Servier (Australia), personal fees from Allergan, Inc., personal fees from Medscape (WebMD), personal fees from CME Institute (Physicians Postgraduate Press, Inc.), personal fees from CMEology, personal fees from American Psychiatric Association Publishing, personal fees from Hogrefe Publishing, personal fees from Jones and Bartlett, personal fees from Wolters Kluwer Health (UpToDate), outside the submitted work.

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Data Sharing

We would make the deidentified participant data and associated documentation (e.g., data dictionaries, trial protocol) available to users only under a formal data sharing and use agreement that provides for a commitment to the following: [1] using the data only for research purposes and not to identify any individual participant, [2] securing the data using appropriate computer technology, [3] destroying or returning the data after analyses are completed, [4] accepting reporting responsibilities, [5] abiding by restrictions on redistribution of the data for commercial purposes or to third parties, and [6] proper acknowledgement of the data resource. In addition, appropriate fees may be assessed upon mutual agreement on requests for information in a format other than that we intend to provide. We will not be responsible for providing any analytical support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ebiom.2021.103387.

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