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Neural and behavioral markers of inhibitory control predict symptom improvement during internet-delivered cognitive behavioral therapy for depression

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Poor inhibitory control contributes to deficits in emotion regulation, which are often targeted by treatments for major depressive disorder (MDD), including cognitive behavioral therapy (CBT). Brain regions that contribute to inhibitory control and emotion regulation overlap; thus, inhibitory control might relate to response to CBT. In this study, we examined whether baseline inhibitory control and resting state functional connectivity (rsFC) within overlapping emotion regulation-inhibitory control regions predicted treatment response to internet-based CBT (iCBT). Participants with MDD were randomly assigned to iCBT ($N = 30$) or a monitored attention control (MAC) condition ($N = 30$). Elastic net regression was used to predict post-treatment Patient Health Questionnaire-9 (PHQ-9) scores from baseline variables, including demographic variables, PHQ-9 scores, Flanker effects (interference, sequential dependency, post-error slowing), and rsFC between the dorsal anterior cingulate cortex, bilateral anterior insula (AI), and right temporoparietal junction (TPJ). Essential prognostic predictor variables retained in the elastic net regression included treatment group, gender, Flanker interference response time (RT), right AI-TPJ rsFC, and left AI-right AI rsFC. Prescriptive predictor variables retained included interactions between treatment group and baseline PHQ-9 scores, age, gender, Flanker RT, sequential dependency effects on accuracy, post-error accuracy, right AI-TPJ rsFC, and left AI-right AI rsFC. Inhibitory control and rsFC within inhibitory control-emotion regulation regions predicted reduced symptom severity following iCBT, and these effects were stronger in the iCBT group than in the MAC group. These findings contribute to a growing literature indicating that stronger inhibitory control at baseline predicts better outcomes to psychotherapy, including iCBT.

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INTRODUCTION

Deficits in executive functioning (EF), a heterogenous construct that encompasses processes including working memory, cognitive flexibility, and inhibitory control, are a prominent, clinically important feature of major depressive disorder (MDD) [1]. EF deficits are identifiable by the first depressive episode [2], persist in remitted patients [2, 3], do not significantly improve with antidepressant treatment [4], and are more severe following multiple episodes [5], suggesting that they may be either a vulnerability marker or a persistent consequence of MDD [2]. EF deficits can interfere with successful emotion regulation. Emotion regulation, a central skill in psychotherapy, including cognitive behavioral therapy (CBT), is the process of managing emotions through the application of any of several different strategies (e.g., cognitive reappraisal) [6], and it is of interest for MDD because symptoms of depression, such as excessive sadness, hopelessness, and the loss of positive mood, are signs of poor emotion regulation.

Overall, the existing literature suggests that poor baseline EF may be a prognostic marker signaling increased risk of poor treatment response [7, 8]. Few studies have examined EF as a predictor of response to psychotherapy in particular, including CBT, although there is some converging evidence that poor EF also predicts worse outpatient treatment response with psychotherapy or psychotropic medication [9] (though see [10]). Given their prevalence and persistence, it is important to understand how EF deficits in MDD may contribute to relapse, remission, and response to treatment. Specific aspects of EF may be particularly vulnerable in MDD. Inhibitory control is particularly relevant to MDD because successful emotion regulation requires an individual to inhibit the processing of negative information and disengage from negative information [11]. Poor inhibitory control then sets the stage for persistent low mood, the hallmark of depression.

Inhibitory control in MDD has been frequently assessed using the Flanker task, which measures selective attention, a subtype of inhibitory control that involves top-down, voluntary maintenance of goals to suppress attention to other stimuli [12, 13]. In the arrow Flanker task, participants must indicate the direction of a central

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"target" arrow surrounded by flanking arrows that either face in the same ('congruent': >>>>> or <<<<<) or opposite directions ('incongruent': >><>> or <<><<). The premise is that incongruent trials require greater inhibitory control because of the need to suppress conflicting information from the flankers [14]. Although the Flanker task does not classically contain emotionally valenced stimuli, "cold" and "hot" cognitive processes are not independent [15], and the Flanker task probes processes associated with emotion regulation. Notably, better Flanker performance is associated with greater likelihood of choosing reappraisal, a key emotion regulation strategy emphasized in CBT, over distraction [16].

The behavioral Flanker literature in MDD is mixed and group differences in Flanker interference effects compared to healthy controls (HC) have usually not been found [17–19]. However, more nuanced measures may be more sensitive to MDD deficits [20]. Post-error behavioral adjustments and analysis of sequential dependencies are two such measures. Following a trial on which an error occurs, healthy individuals typically slow (increase) their response time (RT) (the Rabbitt effect) and may also increase their accuracy (the Laming effect) [21]. These post-error adjustments may reflect the implementation of cognitive control following an error, orienting to an unexpected event (i.e., the error), increased motor inhibition, reduced sensitivity to sensory-perceptual information, and/or an increased threshold for the amount of evidence that must be accumulated to make a decision [22–25]. Healthy individuals also tend to perform better (more accurate, faster RT) on an incongruent trial when the incongruent trial follows another incongruent trial (i-i) than when it follows a congruent trial (c-i), a phenomenon called the Gratton effect [26]. The Gratton effect is thought to occur because an incongruent trial triggers the anterior cingulate cortex (ACC) to increase top-down control and increase attention to the target [27, 28], or due to priming of the association between the stimulus and response on the first trial [21, 29]. Individuals with MDD symptoms do not show typical post-error adjustments, possibly due to elevated affective responses to mistakes [30, 31], and show weaker Gratton effects [32] (though see [20, 31, 33]). Consistent with the general association between better baseline inhibitory control and better treatment outcomes, more normative post-error performance at baseline has been associated with greater symptom improvement following partial hospital treatment for MDD [34] (though see [20] for a negative finding on post-error group differences).

In contrast to the mixed behavioral literature, there is stronger evidence that neural alterations in inhibitory control systems occur in MDD and predict treatment outcomes. Neuroimaging methods may be more sensitive to subtle inhibitory control deficits that are not evident in behavioral data due to compensatory processes [35]. Individuals with MDD tend to show hypoactivity of inhibitory control brain regions [36, 37]. When MDD participants perform similarly to healthy individuals on inhibitory control tasks, they tend to demonstrate hyperactivity in prefrontal regions [38, 39]. Accordingly, when individuals with depression and HC showed similar error rates, individuals with depression showed greater dorsal ACC (dACC) activation on incorrect versus correct incongruent NoGo trials on a Flanker Go/NoGo task compared to HC, which may represent compensatory efforts and/or hypersensitivity to negative feedback [40]. Moreover, a growing literature demonstrates that brain regions implicated in inhibitory control overlap with those involved in emotion regulation [41, 42]. Because affective responses and motivation contribute to inhibitory control deficits, dysfunction in emotion regulation brain regions may also contribute to inhibitory control deficits in MDD. In particular, regions involved in inhibitory control and emotion regulation include portions of the anterior temporo-parietal junction (TPJ), anterior insula (AI), dACC, and inferior and middle frontal gyri [41, 42]. The dACC and inferior and middle frontal gyri have commonly been implicated in inhibitory control and emotion regulation [36, 41]. Although the AI and TPJ are heterogeneous brain regions involved in a number of different brain networks and functions, they are hubs that facilitate the engagement of appropriate brain networks for specific tasks, a function central to cognitive control [43, 44].

These overlapping regions are of particular interest because CBT aims to improve inhibitory control over emotional thoughts and processes (e.g., through teaching emotion regulation strategies like cognitive reappraisal). Critically, these overlapping inhibitory control-emotion regulation regions also form a resting state network [41, 45]. Resting state functional connectivity (rsFC) reflects the intrinsic connections between regions. Functionally connected brain regions exhibit synchronized activity at rest and the brain at rest uses 20% of bodily energy [46]. Brain energy consumption changes minimally with a task (5% or less [47]) and rsFC minimizes the potential confound of task performance, like reaction time or number of errors, on brain metrics [48]. As such, rsFC is a promising measure to probe the role of inhibitory control-emotion regulation regions in depression and treatment response. Indeed, rsFC within this shared network is related to inhibitory control behavioral performance [49, 50]. Specifically, greater dACC-supplementary motor area rsFC was related to neural markers of hyperresponsivity to errors [49] and greater dACC-dorsolateral prefrontal cortex (dlPFC) and insula-dlPFC rsFC was associated with lower conflict adaption or Gratton effect [50]. While prior studies have identified ACC activity as a predictor of treatment response in MDD [51–53], fewer studies have examined functioning throughout the overlapping inhibitory control-emotion regulation network. In one prior study, baseline rsFC between the right insula and right middle temporal gyrus was a significant predictor of symptom improvement during behavioral activation treatment for depression [54], though there was no comparison condition or placebo treatment.

Given CBT's emphasis on cognitive restructuring and emotion regulation, we hypothesized that baseline inhibitory control and/or functioning within inhibitory control networks might relate to response to CBT. One implementation of CBT of growing importance due to its scalability (i.e., ability to reach many individuals at minimal cost) and increasingly widespread use is internet-based CBT (iCBT), which addresses multiple barriers to treatment access [55]. Studies of iCBT have identified factors associated with better treatment response [55–57] but, to date, we are not aware of studies relating baseline cognitive performance, and especially inhibitory control, to iCBT treatment response. Indeed, the literature on inhibitory control predicting response to CBT or psychotherapy is limited. Existing studies generally lack control groups, which makes it difficult to differentiate effects related to natural recovery vs. treatment-specific effects.

In sum, we investigated putative predictors of treatment response in participants with MDD enrolled in a randomized controlled trial of iCBT vs. a monitored attention control (MAC) condition. The set of predictors included behavioral measures of Flanker task performance, including the Flanker interference effect on accuracy and RT plus measures of post-error performance (Rabbitt-Laming effects) and sequential dependency (Gratton effects), together with rsFC between inhibitory control-emotion regulation network regions [42]. We hypothesized better Flanker performance and stronger rsFC between inhibitory control-emotion regulation network regions at baseline would predict better treatment response, and these effects would be stronger in the iCBT vs. MAC condition.

METHODS AND MATERIALS

Participants

Informed consent was obtained from two hundred sixty-six (266) participants to participate in the study. This study (ClinicalTrials.gov Identifier: NCT01598922) was approved by the Institutional Review Boards of McLean Hospital and Partners Healthcare and was conducted in

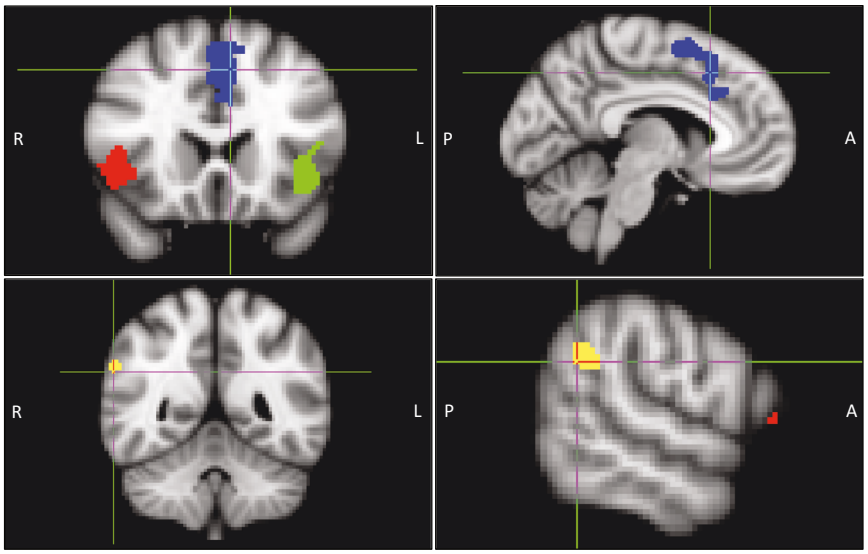

Fig. 1 Locations of regions of interest (ROIs). Note. Blue: dorsal anterior cingulate cortex (dACC). Red: right anterior insula (AI). Green: left AI. Yellow: right temporoparietal junction (TPJ). ROIs were derived from Langner et al. [42], (Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control: http://anima.fz-juelich.de/studies/Langner_2018). The conjunction map for meta-analyses of cognitive emotion regulation (CER) and cognitive action regulation (CAR) was downloaded (CER_and_CAR_cFWE05.nii.gz, from http://anima.fz-juelich.de/studies/Langner_2018).

accordance with the Declaration of Helsinki. The study entailed an initial screening visit (baseline assessment of symptoms, neuroimaging, and cognition), a 10-week iCBT treatment protocol, and a second in-person assessment. Inclusion criteria included primary diagnosis of current MDD and mild to moderate/severe self-reported depression scores on the Patient Health Questionnaire-9 (PHQ-9) [58] between 10 and 23. No participants were taking psychotropic medications. Participants who did not complete the treatment (iCBT: $n = 7$; MAC: $n = 10$) and one participant who inconsistently reported psychiatric history were excluded. In total, data from 60 participants were included (iCBT: $n = 30$; MAC: $n = 30$). See supplement for full inclusion/exclusion criteria, consort diagram, and comparisons between those who prematurely discontinued treatment and those who completed treatment.

Treatment and self-report questionnaire (PHQ-9)

The goal of the overarching treatment study was to investigate whether iCBT would be more effective than MAC at improving depression symptoms, reducing negative cognitive biases, and normalizing brain functioning. This manuscript reports analyses of secondary outcomes to explore predictors of iCBT response. The original report of the treatment study described primary outcomes, and secondary outcomes related to volumetric findings were previously described; for full description of clinical procedures and outcomes, including attrition and the original clinical trial's CONSORT diagram, please refer to these prior reports [57, 59]. Briefly, participants were randomly assigned to MAC or iCBT. Participants completed six online 'lessons' over a ten-week study period. At the start of each lesson, all participants completed symptom questionnaires, including the PHQ-9 [58]; for the MAC group, this was the full extent of their lessons. Participants in iCBT then completed six online CBT lessons along with weekly homework assignments.

The PHQ-9 is a self-report questionnaire assessing the 9 DSM-IV criteria for MDD (see supplement for more details) [58]. Although the Hamilton Rating Scale for Depression (HAMD) was also collected and was the primary outcome measure of this study's original report [59], we focus on the PHQ-9 to increase the relevance of results to real-world implementation of online psychotherapy, which is more likely to utilize self-report as opposed to clinician rating scales. Because the HAMD is a gold-standard depression assessment, we also examined the HAMD as an outcome variable; please see the Results section and supplement for more details.

Flanker task

Participants completed a modified Eriksen Flanker task outside of the scanner. Participants completed 30 practice trials and then five blocks, each consisting of 70 trials (46 congruent, 24 incongruent). See the supplement and Supplementary Table S1 for further details regarding the task and formulas for the output variables. Higher Flanker interference scores indicate more interference on incongruent trials (i.e., worse inhibitory control). Higher Gratton scores reflect greater ability to sustain selective attention across consecutive incongruent trials (better inhibitory control). Higher post-error adjustment scores reflect greater post-error adjustments (better inhibitory control).

Resting state fMRI

A Siemens Tim Trio scanner (3.0 Tesla: Siemens, Erlangen, Germany) was used with a 32-channel head coil. Preprocessing was performed using SPM8 (update revision number 4667: http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Denoising and subsequent analytic steps were performed in the CONN toolbox (version 15.d: https://www.nitrc.org/projects/conn/) [60]. Further details of MRI image acquisition and resting state processing are presented in the supplement.

Regions of interest (ROIs) were derived from a meta-analysis by Langner et al. [42]. The conjunction map for meta-analyses of cognitive emotion regulation (CER) and cognitive action regulation (CAR) was downloaded (CER_and_CAR_cFWE05.nii.gz, from http://anima.fz-juelich.de/studies/Langner_2018). The map was subdivided into four contiguous clusters: right AI, left AI, frontal medial, and right TPJ (Fig. 1) and binarized. Pearson correlations between the time courses of the four ROIs were computed, and Fisher's z-transformed values were extracted for further analysis. These regions do not overlap with those in our prior report of rostral ACC morphometry as a predictor of iCBT treatment response [57].

Statistics

We imputed missing baseline data using a random forest based algorithm (missForest) [61, 62]. Missingness ranged from 0% (age, treatment group, gender, race, baseline PHQ-9, post-treatment PHQ-9) to 15% (rsFC). We also imputed data for Flanker variables that failed quality control (QC) metrics (7 Gratton and 12 post-error QC failures). We conducted chi-squared and *t*-tests to compare the iCBT to MAC groups on demographic variables (age, gender), baseline and post-treatment PHQ-9 scores, Flanker performance, and rsFC. Numeric variables were standardized using R's scale function. We implemented elastic net regression (glmnet) [63] in R to predict post-treatment PHQ-9 scores using baseline variables. An elastic net regression selects variables to retain in the model while applying two penalties to avoid overfitting. We used 10-fold cross-validation (i.e., we split the data into ten subsets and each subset was used as a testing dataset while the remaining data was used as the training dataset) to select weights for the L1 and L2 penalties (α) as well as the overall strength of the penalty (λ). In each model, entered variables included independent variables (described below) and the interactions between treatment group

Table 1. Demographic information and descriptive statistics.

	MAC group ($n = 30$)				iCBT group ($n = 30$)				
	Mean (SD)	Skew	Kurtosis	SE	Mean (SD)	Skew	Kurtosis	SE	
Age	29.31 (7.01)	0.50	−0.89	1.28	29.86 (7.86)	0.76	−0.47	1.44	$t = -0.29$, $p = 0.78$
Gender (F/M)	(21/9)				(17/13)				$X^2 = 0.65$, $p = 0.42$
Baseline PHQ-9	14.63 (3.55)	0.32	−0.39	0.65	13.33 (3.69)	−0.14	−0.80	0.67	$t = 1.39$, $p = 0.17$
Post Treatment PHQ-9	10.63 (4.60)	−0.08	−0.23	0.84	7.13 (5.16)	0.62	−0.49	0.94	$t = 2.77$, $p = 0.01$*
Flanker accuracy	0.22 (0.12)	0.47	−0.85	0.02	0.20 (0.14)	0.60	−0.85	0.02	$t = 0.77$, $p = 0.44$
Flanker RT	89.84 (15.45)	0.68	−0.38	2.82	86.14 (19.32)	0.91	0.92	3.53	$t = 0.82$, $p = 0.42$
Gratton accuracy	0.06 (0.12)	−0.50	−0.20	0.02	0.08 (0.06)	0.00	−0.77	0.01	$t = -0.62$, $p = 0.54$
Gratton RT	−3.71 (21.52)	−0.32	1.49	3.93	0.88 (17.07)	−0.63	0.88	3.12	$t = -0.92$, $p = 0.36$
Post-error accuracy	0.00 (0.04)	−0.14	0.23	0.01	-0.01 (0.03)	−0.54	0.15	0.01	$t = 0.61$, $p = 0.55$
Post-error RT	7.90 (23.46)	−0.09	0.09	4.28	6.79 (16.55)	−0.58	0.33	3.02	$t = 0.21$, $p = 0.83$
dACC-left AI rsFC	0.64 (0.24)	−0.47	−0.55	0.04	0.67 (0.18)	0.27	−1.09	0.03	$t = -0.41$, $p = 0.68$
dACC-right AI rsFC	0.53 (0.20)	−0.26	−0.25	0.04	0.57 (0.21)	−0.33	−0.27	0.04	$t = -0.83$, $p = 0.41$
dACC-TPJ rsFC	0.11 (0.20)	0.20	−0.13	0.04	0.14 (0.20)	0.80	1.31	0.04	$t = -0.51$, $p = 0.61$
Right AI-left AI rsFC	0.64 (0.25)	0.20	−0.24	0.05	0.79 (0.21)	−0.61	0.26	0.04	$t = -2.50$, $p = 0.02$*
Left AI-TPJ rsFC	0.17 (0.20)	0.09	−0.51	0.04	0.19 (0.20)	0.70	0.20	0.04	$t = -0.29$, $p = 0.77$
Right AI-TPJ rsFC	0.39 (0.23)	0.01	−0.79	0.04	0.38 (0.15)	−0.65	0.58	0.03	$t = 0.15$, $p = 0.88$

MAC monitored attention control, *iCBT* internet-based cognitive behavioral therapy, *SD* standard deviation, *SE* standard error, *F* female, *M* male, *PHQ-9* patient health questionnaire-9, *RT* response time, *dACC* dorsal anterior cingulate cortex, *AI* anterior insula, *rsFC* resting state functional connectivity, *TPJ* temporoparietal junction.
For all *t*-tests, the degree of freedom is 58; for the Chi-squared test, the degree of freedom is 1. For participant race and ethnicity: across the combined sample, participants reported that they were white (63.3%), Asian (13.3%), Black (5%), more than one race (5%), other (3.3%), unknown (10%); 10% reported Hispanic ethnicity, 31.7% did not provide ethnicity information, and 43.3% reported non-Hispanic ethnicity.

(iCBT vs MAC) and all independent variables. We implemented a three-stage approach to build the predictive model to determine which sets of variables are most predictive of post-treatment depression scores. In Stage 1, we conducted elastic net regressions with demographic/treatment variables (age, gender, treatment group, and baseline PHQ-9 score) and Flanker performance variables. In Stage 2, we replaced the Flanker variables in Stage 1 with emotion regulation-inhibitory control network rsFC variables. Variables retained in Stages 1 and 2 were entered in Stage 3, examining both Flanker and rsFC variables. In each stage, to account for the variability of variable selection, we repeated the elastic net regression analysis (which includes both the selection of α and λ and the estimation of regression coefficients) 10,000 times and calculated the proportion of replicates in which a covariate had a non-zero regression coefficient. A variable was retained if the proportion was equal to or greater than 0.75 (i.e., had a non-zero regression coefficient in at least 7500 replicates). Because we are using the elastic net regression to build a prediction model, we report the proportion of replicates with non-zero coefficients; we do not report *p*-values. We include the confidence intervals and *p*-values in the supplement; of note, the testing results, however, are not accurate because the testing and training datasets overlap so although these *p*-values are all greater than 0.05, these variables still contribute to the prediction accuracy. In interpreting our results, we focus on variables with absolute value coefficients that exceed the average absolute value coefficient of all retained variables at each stage; variables below this threshold were considered non-essential predictors. See Supplementary Table S2 for results of the non-essential predictors. To evaluate the prediction performance of the three models, we additionally performed 10-fold cross-validation (on top of the 10-fold cross-validation for hyper-parameter tuning) during each of the 10,000 runs of the elastic net. During each run, we calculated the mean squared error (MSE) of the prediction for the fold for the three models, as well as the MSE for the prediction of a null model without any variables as predictors (i.e., by simply calculating the MSE for the test set minus the mean of the training set). We calculated the mean MSE of the elastic net regressions for the three stages and the null model over the 10,000 runs. We compared the mean MSEs of the different models to the null model and to the other elastic net models using corrected *t*-tests [64]. Finally, we fit an additional ordinary least squares linear regression model to the data with the essential predictors retained in Stage 3 to understand the associations of these variables to post-treatment PHQ-9 scores. Partial regression plots were generated to illustrate the adjusted effects of each retained variable using the 'effects' package in R; confidence bands are +/− the standard error of the fit.

RESULTS

Demographics and descriptive statistics

The MAC group had lower baseline right AI-left AI rsFC ($t(58) = 2.50$, $p = 0.015$) and, as previously reported [59], higher post-treatment PHQ-9 scores ($t(58) = 2.77$, $p = 0.007$) than the iCBT group. There were no other significant group differences. See Table 1.

Flanker behavioral results

Across both groups, the Flanker interference effects were significant for accuracy ($t(59) = 12.84$, $p < 0.001$, $d = 1.66$) and RT, $t(59) = 39.08$, $p < 0.001$, $d = 5.04$. The Gratton effect was significant for accuracy ($t(59) = 5.80$, $p < 0.001$, $d = 0.75$) but not RT, $t(59) = -0.57$, $p = 0.57$, $d = 0.07$. The post-error effect was significant for RT ($t(59) = 2.82$, $p = 0.006$, $d = 0.36$) but not for accuracy, $t(59) = -1.16$, $p = 0.25$, $d = 0.15$.

Elastic net regressions predicting post-treatment PHQ-9 scores

Stage 1: Inhibitory control performance as predictors of symptom change. We entered demographic and treatment variables (age, gender, treatment group, and baseline PHQ-9 score) into the model, along with Flanker accuracy, Flanker RT, Gratton accuracy, Gratton RT, post-error accuracy, and post-error RT. Essential retained variables included treatment group; gender; and the interactions between treatment group and: gender, Flanker RT, Gratton accuracy, and post-error accuracy (Table 2; see Supplementary Table S2 for a complete list of retained variables).

Stage 2: rsFC within inhibitory control-emotion regulation network regions as predictors of symptom change. We entered

Table 2. Variables retained in elastic net regressions predicting post-treatment PHQ-9 scores.

Variable	Proportion of replicates with non-zero coefficients
Stage 1	
Tx group	1.0000
Gender	0.9774
Tx group * Gender	0.9829
Tx group * Flanker RT	1.0000
Tx group * Gratton accuracy	1.0000
Tx group * Post-error accuracy	1.0000
Stage 2	
Tx group	1.0000
Right AI-TPJ rsFC	1.0000
Tx group * Age	1.0000
Tx group * Gender	0.9988
Tx group * Right AI-TPJ rsFC	1.0000
Stage 3	
Tx group	1.0000
Gender	0.9987
Flanker RT	1.0000
Right AI-TPJ rsFC	1.0000
Right AI-Left AI rsFC	1.0000
Tx group * Baseline PHQ-9	0.9999
Tx group * Age	1.0000
Tx group * Gender	1.0000
Tx group * Flanker RT	1.0000
Tx group * Gratton accuracy	1.0000
Tx group * Post-error accuracy	1.0000
Tx group * Right AI-TPJ rsFC	1.0000
Tx group * Right AI-Left AI rsFC	1.0000

For interpretation, only variables with absolute value coefficients that exceed the average absolute value coefficient of all retained variables at each step are included in this table. See supplementary Table S2 for a complete list of retained variables and proportion of replicates with non-zero coefficients.
Tx treatment, *PHQ-9* patient health questionnaire-9, *RT* response time, *AI* anterior insula, *rsFC* resting state functional connectivity, *TPJ* temporoparietal junction.

demographic and treatment variables (age, gender, treatment group, and baseline PHQ-9 score) into the model, along with rsFC values among dACC, left AI, right AI, and TPJ ROIs. Essential retained variables included treatment group; right AI-TPJ rsFC; and the interactions between treatment group and: age, gender, and right AI-TPJ rsFC (Table 2).

Stage 3: Inhibitory control performance and rsFC in inhibitory control-emotion regulation network regions as predictors of symptom change. We entered baseline PHQ-9 scores into the model, along with variables retained at Stage 1 and Stage 2, including age, treatment group, gender, Flanker accuracy and RT, Gratton accuracy and RT, post-error accuracy and RT, dACC-TPJ rsFC, dACC-left AI rsFC, right AI–TPJ rsFC, and left AI–right AI rsFC. Essential retained variables included treatment group; gender; Flanker RT; right AI-TPJ rsFC; left AI-right AI rsFC; and the interactions between treatment group and: baseline PHQ-9, age, gender, Flanker RT, Gratton accuracy, post-error accuracy, right AI–TPJ rsFC, and left AI-right AI rsFC (Table 2).

Model comparisons. The Stage 3 model ($MSE_{Stage3} = 0.89$) had a significantly lower MSE than the null ($MSE_{Null} = 0.99$; $M_{diff} = -0.098$, $SD_{diff} = 0.31$, $t = -3.14$, $p = 0.0017$), Stage 1 ($MSE_{Stage1} = 0.94$; $M_{diff} = -0.042$, $SD_{diff} = 0.21$, $t = -2.73$, $p = 0.0062$), and Stage 2 models ($MSE_{Stage2} = 0.99$; $M_{diff} = -0.092$, $SD_{diff} = 0.28$, $t = 3.43$, $p = 0.00059$). The MSE values of the Stage 1 ($p = 0.071$) and Stage 2 ($p = 0.91$) models did not significantly differ from the null model.

Linear model and directionality of effects for variables retained in the Stage 3 model

We conducted a non-penalized linear regression using the variables retained in the Stage 3 model to obtain non-penalized coefficients estimates (see Fig. 2); overall, the model explained 46% of the variance in post-treatment PHQ-9 scores ($R^2 = 0.46$), $F(17, 42) = 2.07$, $p = 0.03$.

Higher Flanker RT (worse inhibitory control) was associated with higher post-treatment depression severity. This was qualified by an interaction with treatment group; the effect was in the same direction for both groups but stronger in iCBT than MAC (Fig. 3a).

Higher post-treatment depression severity also was associated with weaker right AI-left AI rsFC and stronger right AI-TPJ rsFC. Again, the effects were in the same direction in both groups but stronger in iCBT than MAC (Fig. 3d, e).

In addition, treatment group interacted with post-error and congruency sequence effects. Higher post-treatment depression severity was associated with lower Gratton accuracy (worse inhibitory control; Fig. 3b) but higher post-error accuracy (Fig. 3c) in the iCBT group only.

Supplemental analyses

In the Supplement, we report first-order Pearson correlations between Baseline PHQ-9, Flanker, and rsFC variables and summarize several control analyses: (1) results with all variables entered in a single step, which were essentially identical to the stagewise analysis, (2) Stage 3 results controlling for a more comprehensive set of clinical variables, which were essentially identical to the stagewise analysis; (3) results in the restricted sample ($N = 37$) of individuals without missing data, which, as expected in this smaller, biased sample, were slightly different, but confirmed retention of Flanker variables as essential predictors; (4) results with baseline PHQ-9 scores as the outcome measure, which retained Flanker variables as essential predictors; (5) results with the HAMD as the outcome measure, which were similar but not identical given different clinical correlates of PHQ-9 and HAMD and confirmed retention of Flanker RT as an essential predictor; and (6) results with response status (defined as a ≥ 50% reduction in PHQ-9 scores) as the outcome measure, which, as expected due to the lower variance of the binary response status variable, were similar but not identical.

DISCUSSION

In summary, a set of variables related to inhibitory control at baseline predicted treatment outcomes in participants with MDD in a randomized controlled trial of iCBT. Weaker Flanker RT interference effects were associated with greater improvement in depression, and these effects were stronger in the iCBT than MAC group. In the iCBT but not MAC group, treatment outcomes were positively predicted by the Gratton accuracy effect but, surprisingly, negatively predicted by post-error accuracy. Additionally, lower right AI-TPJ rsFC and higher right AI-left AI rsFC were associated with greater improvements in depression, and these effects were stronger in the iCBT than MAC group.

Although participants in the current study showed some evidence of behavioral inhibitory control abnormalities at baseline (e.g., no Gratton effect on RT), they also showed some normative patterns, including the Gratton effect for accuracy and Rabbitt

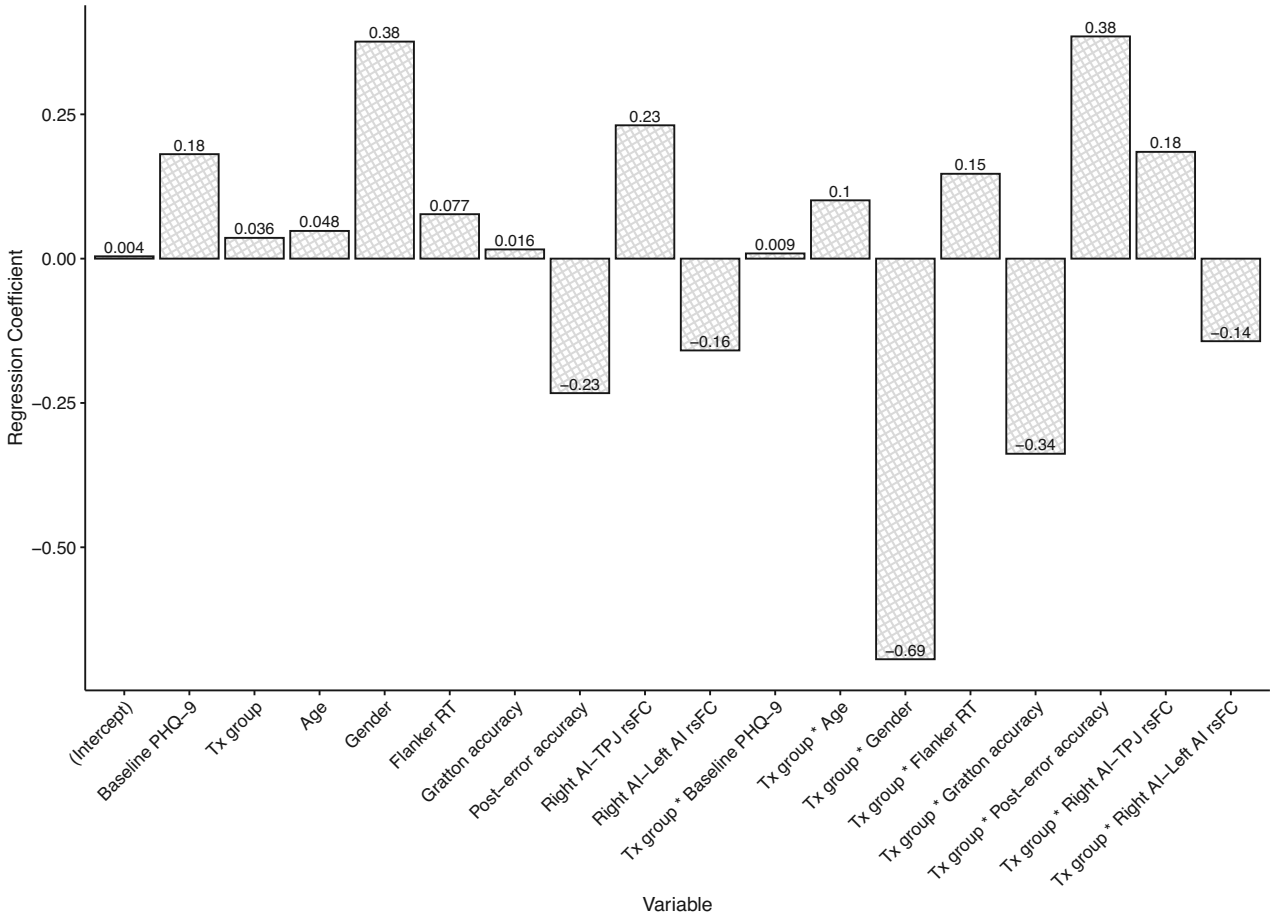

Fig. 2 Plot of linear regression coefficients for model predicting post-treatment PHQ-9 scores, including essential variables retained in the elastic net regression (Stage 3). Note. Tx treatment, PHQ-9 patient health questionnaire-9, RT response time, AI anterior insula, rsFC resting state functional connectivity, TPJ temporoparietal junction.

effect. The lack of a healthy control group prevents us from discerning whether these patterns were normative. Better baseline inhibitory control was associated with lower depression severity after treatment. This is consistent with prior literature suggesting that better baseline EF is associated with more favorable treatment outcomes in MDD [9, 65, 66]. To our knowledge, this study is the first to assess EF as a possible prescriptive (i.e., treatment-specific) indicator in a psychotherapy trial for MDD with a robust control condition. Better inhibitory control at baseline was associated with improved response to iCBT specifically (as opposed to non-specific factors shared with the control condition, such as interaction with study staff, and both groups had the same frequency and duration of interaction with study staff). While the Flanker RT effect was present in both groups, it was stronger in the iCBT than MAC group. Similarly, stronger sequential dependency effects on accuracy (better inhibitory control) predicted greater reduction in depression in the iCBT group only. In contrast, lower (worse inhibitory control) post-error accuracy adjustments were associated with *better* iCBT treatment outcomes. We previously found that depressed individuals did not show normal post-error accuracy improvements but instead showed lower accuracy following errors, which may have been related to abnormal affective/emotional responses to perceived mistakes [30, 31]. One possible interpretation of the unexpected direction of the post-error accuracy finding here is that iCBT might have been particularly effective for individuals with MDD who had this particular affective pattern at baseline (hypersensitivity to errors/mistakes). However, we did not explicitly assess hypersensitivity to errors to be able to evaluate this speculation.

Somewhat surprisingly, none of the rsFC variables that involved the dACC ROI were retained as essential predictors in the analysis. Instead, individual differences in rsFC involving the AI were related to differences in psychotherapeutic outcome. Specifically, better outcomes were associated with higher right AI-left AI rsFC and lower right AI-TPJ rsFC at baseline. The right AI is active during both successful and unsuccessful inhibition, and therefore may play a key role in detecting salient environmental features such as stop signals [67]. Salience network activation may ultimately signal a need for increased central executive control, deactivation of the default mode network (DMN), and/or a need for motor slowing [68, 69]. Indeed, the right AI has been associated with switching between the DMN and central executive brain networks [70, 71], and reduced anticorrelation between these networks is associated with treatment response [72, 73]. A recent meta-analysis identified the *left* AI as being involved in cognitive inhibition, while the bilateral AI was involved in inhibiting a prepotent motor response [13]. Stronger left AI-right AI rsFC at baseline may reflect a better capacity to coordinate across components of inhibitory control, including suppression of attentional distractors and/or suppression of motor responses elicited by those distractors. Left AI-right AI rsFC did not correlate with cognitive inhibition at baseline, however. Additionally, better outcomes were associated with lower rsFC between the right AI and TPJ. Deactivation of the TPJ increases inhibitory control, while activation of the TPJ increases reorienting [45]. Low right AI-TPJ rsFC might reflect a system ready to engage inhibitory control processes as opposed to stimulus-driven attentional reorienting. Indeed, at baseline, lower right AI-TPJ rsFC correlated with greater cognitive control (lower Flanker

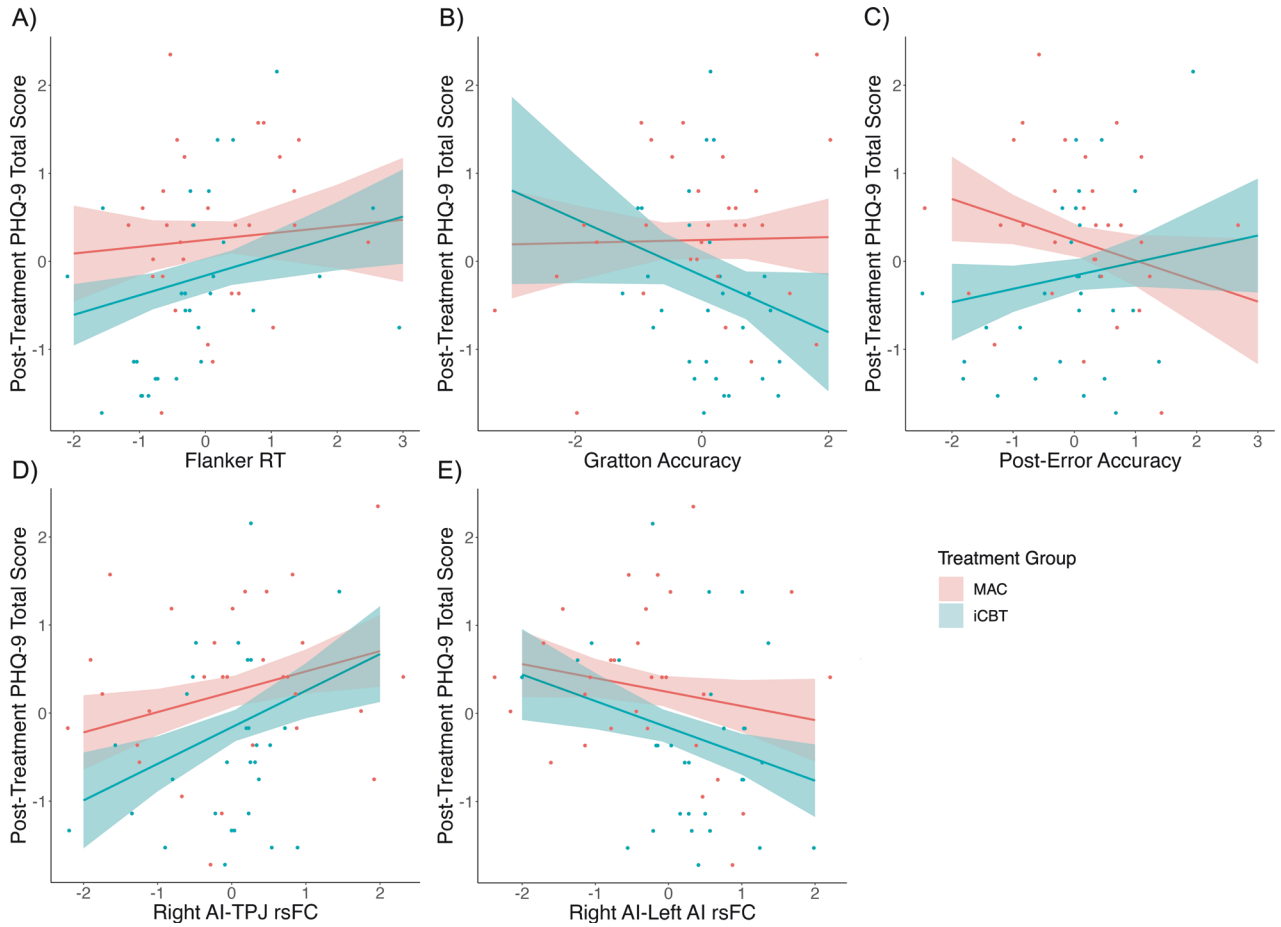

Fig. 3 Partial regressions predicting post-treatment depression by treatment group by Flanker RT, Gratton accuracy, post-error accuracy, right AI-TPJ rsFC, and right AI-left AI rsFC. Note. Partial regressions predicting post-treatment depression by (**A**) Flanker RT by treatment group interaction, (**B**) Gratton accuracy by treatment group interaction, (**C**) post-error accuracy by treatment group interaction, (**D**) right AI-TPJ rsFC by treatment group interaction, and (**E**) right AI-left AI rsFC by treatment group interaction. MAC monitored attention control, iCBT internet-based cognitive behavioral therapy, PHQ-9 patient health questionnaire-9, RT response time, AI anterior insula, TPJ temporoparietal junction, rsFC resting state functional connectivity.

accuracy interference). The TPJ's role in inhibitory control and orienting may explain why better clinical outcomes are associated with *higher* right AI-left AI but *lower* right AI-TPJ rsFC even though the AI and TPJ are within the same network. Finally, the AI also plays a critical role in error monitoring and adapting behavior following errors [74], which may explain its significance as a predictive indicator.

This study has several limitations. First, the iCBT group had (unexpectedly, given the random assignment) higher left AI-right AI rsFC at baseline than the MAC group. Second, strong inhibitory control might lead to better outcomes during iCBT, but other relationships between these variables also are possible. In particular, associations with additional factors such as emotion regulation might explain these findings. Third, replication is needed in a substantially larger sample, particularly for testing interactions. Fourth, it is unknown whether inhibitory control performance and rsFC within inhibitory control networks are associated with treatment response to iCBT beyond this study window (e.g., at 6-month or 12-month follow-ups). Fifth, additional limitations include the use of a self-report measure of symptom severity (see supplemental analyses using HAMD scores) and the fact that it is unknown whether these results would generalize to other treatment modalities. Finally, we focused exclusively on the Flanker and did not include other behavioral tasks. Although we chose the Flanker as it is a known behavioral probe of ACC functioning and the ACC is implicated in treatment response [38], the Flanker does not capture all aspects of inhibitory control, so these findings may not generalize to other measures of inhibitory control.

Together with other studies in the literature identifying predictors of response to different treatments for depression, these findings could potentially help to inform treatment selection for different patients to reduce the number of treatment trials patients must undergo before deriving benefit. Although lack of response to a depression treatment has major costs to the individual patient and society, including uncontrolled symptoms, time, effort, financial costs, and side effects, there is little guidance for personalized treatment selection. Choosing an effective initial treatment is critical given that patients who do not respond to an initial treatment are less likely to benefit from future treatments [75]. Notably, our findings align with other studies predicting treatment response from EF performance, suggesting that more preserved EF is generally associated with better treatment outcomes to antidepressant medications, transcranial direct current stimulation, CBT, and psychodynamic therapy [8]. Of note, ketamine, deep brain stimulation, cognitive rehabilitation, problem-solving therapy and supportive therapy have shown opposite effects with poorer executive functioning being associated with better treatment response, and no associations were found between EF and response to electroconvulsive therapy (ECT; see [8] for a review), suggesting that EF performance may have potential for treatment-specific prediction.

Recent reviews and meta-analyses have implicated rsFC of brain regions outside of our inhibitory control-emotion regulation network in predicting antidepressant treatment response, highlighting the importance of DMN rsFC and subgenual and rostral ACC rsFC in predicting treatment response across a variety of treatments, including transcranial magnetic stimulation (TMS), antidepressant medication, and psychotherapy [76, 77]. However, the majority of participants in this meta-analysis were treated with TMS and antidepressant medication and only 39 subjects participating in CBT were included [76]. Functioning within inhibitory control-emotion regulation regions and the prefrontal cortex (PFC) has been implicated as predictors of treatment response when examining brain functioning during response inhibition and as predictors of CBT response in particular. Greater insula and PFC activation during successful inhibition and dlPFC connectivity during response inhibition have been found to predict treatment response to antidepressant medications [78, 79]. Greater positive subcallosal cingulate-ventrolateral PFC/insula and subcallosal cingulate-ventromedial PFC rsFC was predictive of CBT treatment response (whereas the opposite pattern was found for antidepressant medication) [80]. Electrophysiological indices of intact response inhibition have also been predictive of antidepressant medication and CBT treatment response [81]. These findings along with the current results suggest strong functioning of and pathways among inhibitory control-emotion regulation brain regions may promote response to CBT specifically. Larger studies with comprehensive clinical and neurocognitive assessments randomizing individuals with depression to different treatment modalities are needed to generate and fully test predictive models that can determine which treatment a patient is most likely respond to.

In summary, we have identified a set of predictors of treatment response in unmedicated participants with MDD enrolled in a randomized controlled trial of iCBT, assigned to either iCBT or a control treatment. These predictors included behavioral measures of better inhibitory control as well as worse post-error behavioral adjustments. Additionally, rsFC variables were retained in the model, including connectivity across nodes involved in cognitive control and emotional regulation (particularly right AI-TPJ and right AI-left AI rsFC). Together, these findings contribute to a growing body of literature indicating that stronger inhibitory control at baseline predicts better outcomes during CBT.

DATA AVAILABILITY

Data are available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

William D. S. Killgore, Scott L. Rauch, Isabelle M. Rosso, and Diego A. Pizzagalli conceptualized, designed, and supervised the study. Michelle Thai, Elizabeth A. Olson, and Boyu Ren conducted formal data analysis. Daniel G. Dillon, Christian A. Webb, and Stefanie Nickels contributed to analytic approach. Michelle Thai and Elizabeth A. Olson drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

• MT, IMR, CAW, BR, & WDSK report no biomedical financial interests or potential conflicts of interest. • EAO is an employee of Crisis Text Line, a nonprofit organization.

• Over the past 3 years, Dr. Pizzagalli has received consulting fees from Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sage Therapeutics, Sama Therapeutics, and Takeda; he has received honoraria from the American Psychological Association, Psychonomic Society and Springer (for editorial work) and from Alkermes; he has received research funding from the Bird Foundation, Brain and Behavior Research Foundation, Dana Foundation, Millennium Pharmaceuticals, NIMH, and Wellcome Leap; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. • SLR is employed by Mass General Brigham/McLean Hospital; he is paid as secretary of Society of Biological Psychiatry, and has received payment for Board service to Community Psychiatry/Mindpath Health and also for Board service to National Association of Behavioral Healthcare. He has served as a volunteer member of the Board for Anxiety & Depression Association of America, and The National Network of Depression Centers. He has received royalties from Oxford University Press, Springer Publishing, and American Psychiatric Publishing Inc. He has received research funding from NIMH and the US Army Military Operational Medicine Research Program (Award # W81XWH-12-1-0109; as noted above). • DD has received consulting fees from Pfizer, Inc., and from The Many Brains Project for work unrelated to the current study. • Over the past 3 years, SN was an employee of and owned equity in Verily Life Sciences. • No funding from these entities was used to support the current work, and all views expressed are solely those of the authors.

ADDITIONAL INFORMATION

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Supplement

METHODS

Inclusion/exclusion criteria:

Inclusion criteria included current DSM-IV MDD, mild to moderate/severe depression defined as Patient Health Questionnaire-9 (PHQ-9)[1] score between 10 and 23, age 18 to 45, English fluency, regular access to a phone and computer, absence of psychotropic medications for at least the past 2 weeks (6 weeks for fluoxetine and 6 months for neuroleptics), and right-handedness. Exclusion criteria included suicidal ideation (initial PHQ-9 item 9 score 2 or greater), lifetime bipolar or schizophrenia spectrum disorder, lifetime substance abuse or dependence, current alcohol abuse or dependence, past alcohol dependence, past-year recreational drug use (except cannabis), past month cannabis use, current participation in CBT, history of electroconvulsive therapy, education less than 9 years, and MRI contraindications.

Self-Report Questionnaire (PHQ-9):

The PHQ-9 is a self-report questionnaire assessing the 9 DSM-IV criteria for MDD. PHQ-9 items are scored from 0 to 3, summed to produce a total score between 0 and 27. Initial validation studies demonstrated that the PHQ-9 has adequate internal reliability (Cronbach's alpha = 0.86-0.89), test-retest reliability (0.84), and concurrent validity based upon concordance with clinical interviews.[63] Reduction in PHQ-9 scores in the iCBT group (6.2 point decrease) was comparable to that seen in other recent studies of iCBT for MDD.[64]

Additional questionnaires used in supplemental analyses:

Mood and Anxiety Symptom Questionnaire (MASQ, 62-item brief form). The MASQ is a self-report questionnaire designed to assess Clark & Watson's tripartite model of anxiety and depression, which proposes a nonspecific/overarching negative affect factor, a somatic tension/hyperarousal factor specific to anxiety, and a low positive affect factor specific to depression.[2,3,3,4] Participants provide past-week ratings of intensity of each item from 1 ("very slightly or not at all") to 5 ("extremely"). Subscales used in this study included MASQ Anhedonic Depression (n = 22 items, related to loss of interest (8) and reverse-scored high positive affect (14)) and MASQ Anxious Arousal (n = 17 items) subscales.

Beck Anxiety Inventory (BAI).[5] The BAI is a 21-item self-report questionnaire assessing symptoms of past-week anxiety. Participants rate how much they have been bothered by each symptom during the past week, from 0 ("not at all") to 3 ("severely, I could barely stand it"), summed to produce a total score ranging from 0-63. Validation studies demonstrated that the BAI has adequate internal reliability (Cronbach's alpha = 0.92) and adequate concurrent validity based upon concordance with other self-report measures of anxiety and psychological distress.[6–8]

Flanker task:

Participants completed a modified Eriksen Flanker task on a study laptop outside of the scanner. They first completed a practice session consisting of 30 trials (15 congruent, 15 incongruent). They were instructed to respond as quickly as possible by pressing the 'c' key with their left index finger when the center arrow pointed left (<<<<< or >><>>) or by pressing the 'm' key with their right index finger when the center arrow pointed right (>>>>>, <<><<). For each

individual, the 85th percentile of their practice response time (RT) distribution was used as a deadline for responding during the first block of the actual task.

Prior to the actual task, participants were prompted, “It is very important that you respond as quickly and accurately as possible. To help you stay on track, you will receive negative feedback if you go too slowly. If you respond too slowly, the word “TOO SLOW” will appear on the screen. If you see these words, please try to speed up.” Participants completed five blocks, each consisting of 70 trials (46 congruent, 24 incongruent). The 85th percentile of RT in the prior block was used to establish a response deadline for blocks 2-5; the deadline for block 1 was set based on the practice trials. Each trial consisted of: flanking arrow presentation (100 ms), addition of the central arrow (50 ms), fixation cross (response period: 1400 ms), presentation of TOO SLOW feedback or extended fixation cross (300 ms), and variable duration final fixation cross (200-400 ms). The total trial duration varied from 2050-2250 ms. At the end of each block, participants were given feedback to ensure an acceptable speed-accuracy tradeoff: participants making too few errors on incongruent trials (2 or fewer errors per block) were instructed, “Remember to respond as QUICKLY as possible while still being accurate,” which participants making too many errors on incongruent trials (6 or more per block) were instructed, “Remember to respond as ACCURATELY as possible while still being fast.” If neither applied, the end-of-block screen read, “Please respond as quickly and accurately as possible.”

Quality control: Outlier RTs were defined as those that were implausibly short (< 150 ms), or those greater than 3 standard deviations from the participant’s mean RT (calculated separately for congruent and incongruent trials). These trials were excluded from further analysis. Participants were retained if their data set included: 1) no more than 35 RT outliers, 2) at least 200 congruent and 90 incongruent trials with non-outlier RTs, and 3) congruent and incongruent trial accuracies of at least 50%. For the post-error effects, an additional QC check was the need for at least 6 trials that followed an error on an incongruent trial.[9]

Supplementary Table S1. Flanker task performance summary measures

Flanker interference accuracy	$\%\text{Correct}_{\text{Congruent trials}} - \%\text{Correct}_{\text{Incongruent trials}}$
Flanker interference RT	$\text{Mean RT}_{\text{Incongruent correct trials}} - \text{Mean RT}_{\text{Congruent correct trials}}$
Gratton accuracy	$\%\text{Correct}_{\text{Incongruent trials following correct incongruent trials}} - \%\text{Correct}_{\text{Incongruent trials following correct congruent trials}}$
Gratton RT	$\text{Mean RT}_{\text{Incongruent trials following correct congruent trials}} - \text{Mean RT}_{\text{Incongruent trials following correct incongruent trials}}$
Post-error accuracy	$\%\text{Correct}_{\text{Trials following incorrect incongruent trials}} - \%\text{Correct}_{\text{Trials following correct incongruent trials}}$
Post-error RT	$\text{Mean RT}_{\text{Trials following incorrect incongruent trials}} - \text{Mean RT}_{\text{Trials following correct incongruent trials}}$

Note. RT = response time.

Resting state fMRI:

MR image acquisition: A Siemens Tim Trio scanner (3.0 Tesla: Siemens, Erlangen, Germany) was used with a 32-channel head coil. We collected structural T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) images over 176 sagittal slices (TR / TE / flip angle = 2100ms/2.3ms/12°, 256 × 256 matrix; voxel size = 1.0 × 1.0 × 1.0 mm^3). For resting state fMRI,

180 T2*-weighted echoplanar images (EPI) were collected over 34 transverse interleaved slices (TR / TE / flip angle = 2000ms/30ms/90°) with voxel size = 3.5 x 3.5 x 3.5 mm^3, 224 mm field of view.

Image processing and analysis: Standard preprocessing was performed using SPM8 (update revision number 4667: http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running in MATLAB R2014a. Denoising and subsequent analytic steps were performed in the CONN toolbox (version 15.d: https://www.nitrc.org/projects/conn/).[65]

Participants received standardized instructions before completing the resting state scan ("For this scan, we want you to rest quietly with your eyes open and let your mind wander. Do not move and do not fall asleep. Just let your mind daydream for the next few minutes as the scanner operates. Do you have any questions?").

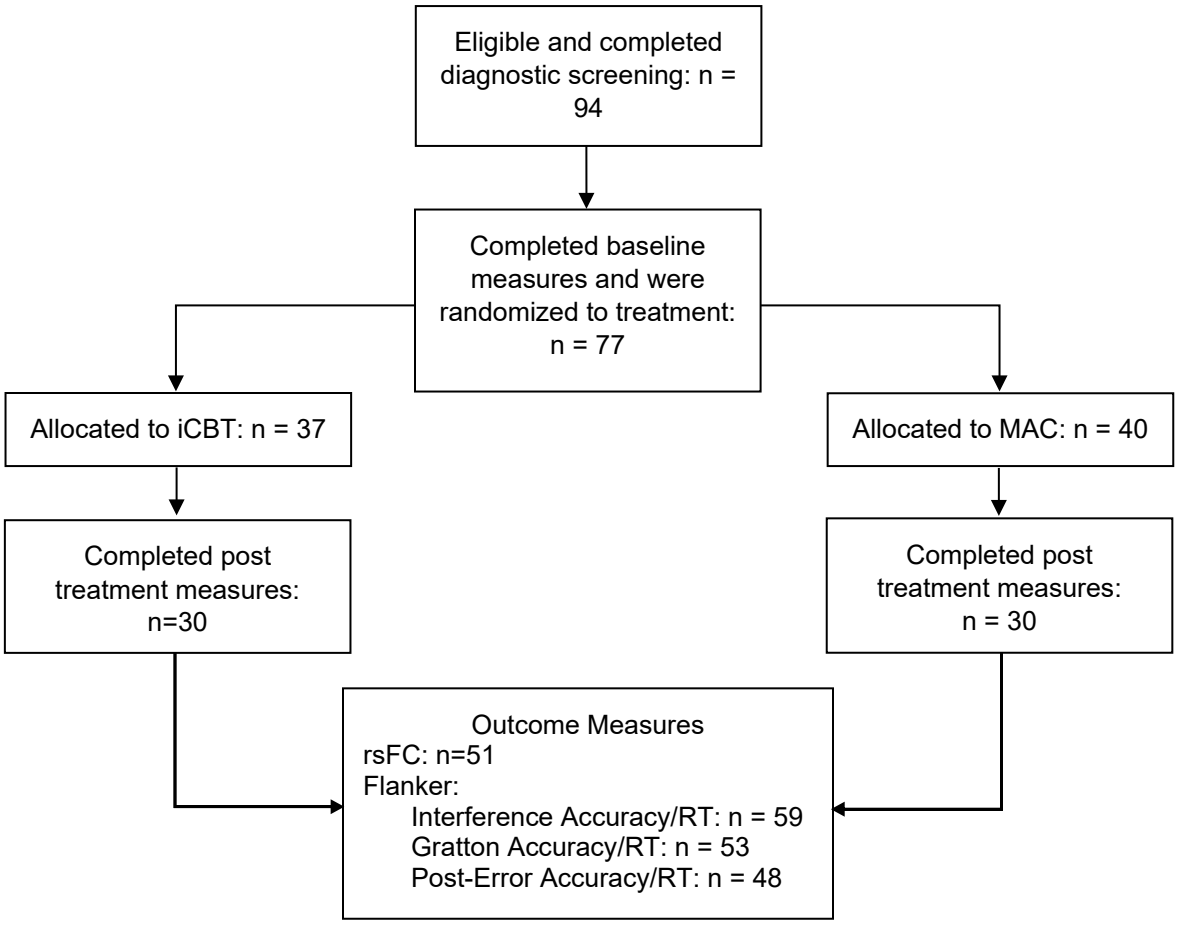
Preprocessing steps included realignment and unwarping, slice timing correction, coregistration to the structural image, segmentation, spatial normalization in Montreal Neurological Institute (MNI) space, smoothing (full-width half maximum [FWHM] = 6mm), and reslicing at 2 x 2 x 2 mm.

For each participant, Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect) was used to identify time points with excessive head motion (> 1 mm from the prior frame) or spikes in global signal intensity (> 3 SD from mean intensity across functional scans). For all subjects, the first volume was flagged as an outlier because of possible field inhomogeneity at the beginning of the scan. Participants with more than 15% flagged volumes were removed from the analysis. Outlier volumes were regressed out during first-level modeling. Additionally, parameters estimating head motion were regressed out at the first level (three translation parameters, three rotation parameters, and one composite parameter reflecting maximum scan-to-scan movement).

Correction for physiological noise (e.g., noise related to cardiac and respiratory activity) was performed in the CONN functional connectivity toolbox (version 15.d: https://www.nitrc.org/projects/conn/;[10]). Sources of noise were estimated using CompCor,[11] which uses principal components analysis to estimate physiological noise from white matter and cerebrospinal fluid and remove it from the BOLD time series. Within CONN, the denoising step therefore included linear regression of the outlier and motion parameters, white matter, CSF, and the main effect of rest as well as its first temporal derivative (to eliminate ramping effects). Following the regression, a band-pass filter (0.008 to 0.09 Hz) was applied to the residual timeseries. The subsequent analysis was performed using the residual BOLD time course at each voxel.

Supplementary Figure S1

Consort Diagram



Note. iCBT = internet-based cognitive behavioral therapy; MAC = monitored attention control; RT = response time; rsFC = resting state functional connectivity.
1 participant was missing Flanker task data, 7 participants failed Flanker and Gratton quality check, and 12 participants failed the Post-Error quality check (i.e., they had less than 7 trials).[9] Participants with imaging data quality issues or more than 15% flagged volumes were removed from the rsfMRI analysis. There were no significant differences in terms of gender, race, and age between those who completed treatment and those who prematurely discontinued treatment, all p's ≥ .10. PHQ-9 depression symptom severity was significantly higher in those who did not complete treatment (M = 17.59, SD = 3.99) compared to those who completed treatment (M = 13.98, SD = 3.65), t(24.13) = 3.35, p = .003.

RESULTS

Supplementary Table S2. All variables retained in elastic net regressions predicting post-treatment PHQ-9 scores

Variable	**Proportion of replicates with**	**Average Coefficient**

	non-zero coefficients	
Stage 1		
Tx group	1	-0.203
Baseline PHQ-9	1	0.066
Age	0.9784	0.033
Gender	0.9774	0.099
Flanker RT	1	0.079
Gratton accuracy	0.8703	0.018
Gratton RT	0.9722	-0.032
Post-error RT	0.9931	-0.047
Tx group * Baseline PHQ-9	0.9983	0.082
Tx group * Age	1	0.082
Tx group * Gender	0.9829	-0.133
Tx group * Flanker accuracy	0.9428	-0.034
Tx group * Flanker RT	1	0.102
Tx group * Gratton accuracy	1	-0.157
Tx group * Post-error accuracy	1	0.121
Tx group * Post-error RT	0.7533	0.018
Stage 2		
Tx group	1	-0.23
Baseline PHQ-9	1	0.103
Age	1	0.074
Gender	0.9845	0.084
dACC-TPJ rsFC	0.9987	-0.03
dACC-Left AI rsFC	0.9959	0.055
Right AI-TPJ rsFC	1	0.124
Right AI-Left AI rsFC	1	-0.084
Tx group * Baseline PHQ-9	0.9164	0.057
Tx group * Age	1	0.16
Tx group * Gender	0.9988	-0.178
Tx group * dACC-TPJ rsFC	0.998	-0.079
Tx group * Right AI-TPJ rsFC	1	0.248
Tx group * Right AI-Left AI rsFC	1	-0.11
Stage 3		
Tx group	1	-0.156
Baseline PHQ-9	1	0.059
Age	1	0.043
Gender	0.9987	0.07
Flanker RT	1	0.065
Gratton accuracy	0.9193	0.007
Gratton RT	0.9999	-0.032
Post-error RT	1	-0.041
Right AI-TPJ rsFC	1	0.072
Right AI-Left AI rsFC	1	-0.066
dACC-TPJ rsFC	0.9926	-0.018
dACC-Left AI rsFC	0.9927	0.028
Baseline PHQ-9 * Tx group	0.9999	0.066
Tx group * Age	1	0.077

Tx group * Gender	1	-0.134
Tx group (MAC) * Flanker accuracy	0.9193	0.007
Tx group * Flanker accuracy	0.9765	-0.031
Flanker RT * Tx group	1	0.076
Tx group * Gratton accuracy	1	-0.128
Tx group (MAC) * Post-error accuracy	1	-0.042
Tx group * Post-error accuracy	1	0.096
Tx group * Post-error RT	0.9194	0.015
Tx group * dACC-TPJ rsFC	0.9896	-0.03
Tx group * Right AI-TPJ rsFC	1	0.124
Tx group * Right AI-Left AI rsFC	1	-0.088

Note. Tx = treatment; PHQ-9 = Patient Health Questionnaire-9; RT = response time; AI = anterior insula; rsFC = resting state functional connectivity; TPJ = temporoparietal junction; dACC = dorsal anterior cingulate cortex.

Supplementary Table S3. Linear regression predicting post-treatment PHQ-9 scores, including essential variables retained in the elastic net regression (Stage 3).

	Post-Treatment PHQ-9		
Predictors	*Estimates*	*CI*	*p*
Intercept	0.004	-0.65 – 0.66	0.991
Baseline PHQ-9*	0.18	-0.19 – 0.55	0.326
Tx group	0.036	-0.87 – 0.94	0.937
Age*	0.048	-0.38 – 0.48	0.822
Gender	0.38	-0.49 – 1.24	0.385
Flanker RT	0.077	-0.41 – 0.56	0.751
Gratton accuracy*	0.016	-0.38 – 0.42	0.934
Post-error accuracy*	-0.23	-0.69 – 0.22	0.310
Right AI-TPJ rsFC	0.23	-0.15 – 0.61	0.225
Right AI-Left AI rsFC	-0.16	-0.55 – 0.23	0.415
Tx group * Baseline PHQ-9	0.009	-0.51 – 0.52	0.972
Tx group * Age	0.1	-0.50 – 0.71	0.737
Tx group * Gender	-0.69	-1.87 – 0.49	0.242
Tx group * Flanker RT	0.15	-0.44 – 0.73	0.615
Tx group * Gratton accuracy	-0.34	-1.13 – 0.46	0.394
Tx group * Post-error accuracy	0.38	-0.23 – 1.00	0.215
Tx group * Right AI-TPJ rsFC	0.18	-0.46 – 0.83	0.565
Tx group * Right AI-Left AI rsFC	-0.14	-0.73 – 0.44	0.626
Observations	60		
R^2 / R^2 adjusted	0.456 / 0.236		

Note. Tx = treatment; PHQ-9 = Patient Health Questionnaire-9; RT = response time; AI = anterior insula; rsFC = resting state functional connectivity; TPJ = temporoparietal junction. See also Figure 1.
*included in linear model although it was not retained in the elastic net because it was part of a retained interaction.

Supplementary Table S4. *Descriptive statistics for additional questionnaires used in supplemental analyses:*

	MAC group (n = 30)				iCBT group (n = 30)				
	Mean (SD)	Skew	Kurtosis	SE	Mean (SD)	Skew	Kurtosis	SE	
MASQ Anxious Arousal	24.10 (7.06)	1.59	2.20	1.29	22.73 (5.29)	1.61	2.46	0.97	t = 0.85, p = 0.40
MASQ Anhedonic Depression	86.57 (8.54)	-0.60	-0.48	1.56	82.33 (7.64)	-0.08	-0.90	1.40	t = 2.02, p = 0.048*
BAI	11.91 (9.08)	0.60	-0.72	1.66	11.60 (6.88)	0.35	-1.10	1.26	t = 0.15, p = 0.88

Note. MAC = monitored attention control; iCBT = internet-based cognitive behavioral therapy; SD = standard deviation; SE = standard error; MASQ = Mood and Anxiety Symptom Questionnaire; BAI = Beck Anxiety Inventory.

For all t-tests, the df is 58.

Supplementary Table S5. *First-order Pearson correlations between Baseline Depression, Flanker variables, and rsFC variables (n = 60)*

	PHQ-9	dACC-left AI	dACC-right AI	dACC-TPJ	Left AI-right AI	Left AI-TPJ	Right AI-TPJ
PHQ-9	1.000	-0.085	-0.207	0.047	-0.199	0.136	-0.066
Flanker RT	0.054	0.192	0.021	-0.154	0.133	0.182	0.211
Flanker Accuracy	-0.010	0.137	0.104	0.018	0.199	0.235	0.260*
Gratton RT	-0.180	0.100	0.152	0.265*	-0.156	0.001	-0.105
Gratton Accuracy	0.044	0.064	-0.020	-0.168	0.234	-0.060	0.192
Post-error RT	-0.235	0.035	0.054	0.067	0.048	0.078	0.175
Post-error Accuracy	0.197	-0.007	-0.024	0.256*	-0.090	0.178	0.233

Note. PHQ-9 = Patient Health Questionnaire-9; RT = response time; dACC = dorsal anterior cingulate cortex; AI = anterior insula; TPJ = temporoparietal junction.

*p < 0.05

A. Entering all variables simultaneously into the elastic net as a single step

As an alternative to the multi-stage process presented here, we explored entering all variables into the model in a single stage. Given the large number of entered variables, we used a lower cutoff (5000 out of 10,000 replicates) to consider a variable retained. We entered basic demographic/treatment variables, including age, gender, treatment group, and baseline PHQ-9 score into the model, along with Flanker performance variables including Flanker accuracy, Flanker RT, Gratton accuracy, Gratton RT, post-error accuracy, and post-error RT; and connectivity values among dACC, left AI, right AI, and TPJ ROIs (n = 32 variables, including interactions and the intercept). The retained variables that exceed the average absolute coefficient of all retained variables (.05) using this approach were largely similar to the essential predictors in Stage 3 in the main manuscript, suggesting that our results were not sensitive to the setup of the multi-stage approach. The only difference compared to the multi-stage approach in the main results was that baseline PHQ-9 emerged as an essential predictor in the single step approach. See Supplementary Table S6.

Supplementary Table S6

Variable	**Proportion of replicates with non-zero coefficients**	**Average Coefficient**
Tx group (MDD)†	1	-0.151
Baseline PHQ-9†	1	0.055
Age	0.9999	0.038
Gender†	0.9857	0.057
Flanker accuracy	0.7829	-0.008
Flanker RT†	1	0.062
Gratton accuracy	0.7852	0.012
Gratton RT	0.9979	-0.03
Post-error accuracy	0.7827	0.008
Post-error RT	0.9998	-0.041
Left AI-TPJ rsFC	0.7827	-0.004
Right AI-TPJ rsFC†	1	0.066
Right AI-Left AI rsFC†	1	-0.058
Dorsal ACC-TPJ rsFC	0.9611	-0.015
Dorsal ACC-left AI rsFC	0.9446	0.025
Dorsal ACC-right AI rsFC	0.7827	-0.009
Tx group (MDD) * Baseline PHQ-9†	0.9999	0.06
Tx group (MDD) * Age†	1	0.071
Tx group (MDD) * Gender†	0.9999	-0.121

Tx group (MDD) * Flanker accuracy	0.845	-0.027
Tx group (MDD) * Flanker RT†	1	0.072
Tx group (MDD) * Gratton accuracy†	1	-0.123
Tx group (MDD) * Gratton RT	0.7827	-0.015
Tx group (MDD) * Post-error accuracy†	1	0.088
Tx group (MDD) * Post-error RT	0.7827	0.012
Tx group (MDD) * Left AI-TPJ rsFC	0.7827	0.017
Tx group (MDD) * Right AI-TPJ rsFC†	1	0.113
Tx group (MDD) * Right AI-Left AI rsFC†	1	-0.083
Tx group (MDD) * Dorsal ACC-TPJ rsFC	0.8943	-0.023
Tx group (MDD) * Dorsal ACC-left AI rsFC	0.783	-0.019
Tx group (MDD) * Dorsal ACC-right AI rsFC	0.9329	-0.016

Note. Tx = treatment; MDD = Major Depressive Disorder; PHQ-9 = Patient Health Questionnaire-9; RT = response time; AI = anterior insula; rsFC = resting state functional connectivity; TPJ = temporoparietal junction; ACC = anterior cingulate cortex. † indicates essential predictors exceed the average absolute coefficient of all retained variables (.05).

B. Cognitive control performance and rsFC in cognitive/emotional control network regions as predictors of symptom change during iCBT (Stage 3), controlling for additional demographic and clinical covariates

At baseline, the MAC group had higher MASQ anhedonic depression scores, p = 0.048 (Table S4); there were no other significant group differences in MASQ or BAI scores. We entered baseline PHQ-9 scores into the model, along with variables retained at Stage 1 and Stage 2, including age, treatment group, Flanker RT, Gratton accuracy, Post-error accuracy, right AI – TPJ rsFC, and left AI – right AI rsFC. Additional covariates included gender, MASQ Anxious Arousal, MASQ Anhedonic Depression, and Beck Anxiety Inventory scores. Essential variables retained in the final model were identical to the essential predictors in the Stage 3 model presented in the main manuscript and included demographic/treatment variables (treatment group and gender); Flanker RT; Right AI-TPJ rsFC; Right AI-Left AI rsFC; and the interactions between treatment group and: Baseline PHQ-9, age, gender, Flanker RT, Gratton accuracy,

post-error accuracy, Right AI-TPJ rsFC, and Right AI-Left AI rsFC. See Supplementary Table S7.

Supplementary Table S7

Variable	**Proportion of replicates with non-zero coefficients**	**Average Coefficient**
Tx group (MDD)†	1	-0.14
Baseline PHQ-9	1	0.051
Age	0.9999	0.041
Gender†	0.9964	0.057
MASQ Anhedonic Depression	0.9963	0.03
MASQ Anxious Arousal	0.9913	0.018
Baseline BAI	0.9497	0.012
Flanker RT†	1	0.062
Gratton accuracy	0.9327	0.006
Gratton RT	0.9994	-0.029
Post-error RT	0.9999	-0.037
Right AI-TPJ rsFC†	1	0.063
Right AI-Left AI rsFC†	1	-0.058
Dorsal ACC-TPJ rsFC	0.9904	-0.016
Dorsal ACC-left AI rsFC	0.9863	0.023
Tx group (MDD) * Baseline PHQ-9†	0.9997	0.061
Tx group (MDD) * Age†	1	0.073
Tx group (MDD) * Gender†	0.9999	-0.12
Tx group (MAC) * Flanker accuracy	0.9327	0.011
Tx group (MDD) * Flanker accuracy	0.9632	-0.026
Tx group (MDD)*Flanker RT†	1	0.072
Tx group (MDD) * Gratton accuracy†	1	-0.116
Tx group (MAC) * Post-error accuracy	0.9999	-0.041
Tx group (MDD) * Post-error accuracy†	1	0.088
Tx group (MDD) * Post-error RT	0.9327	0.008
Tx group (MDD) * Right AI-TPJ rsFC†	1	0.109
Tx group (MDD) * Right AI-Left AI rsFC†	1	-0.082

Tx group (MDD) * Dorsal ACC-TPJ rsFC	0.9769	-0.026

Note. Tx = treatment; MDD = Major Depressive Disorder; PHQ-9 = Patient Health Questionnaire-9; MASQ = Mood and Anxiety Symptom Questionnaire; BAI = Beck Anxiety Inventory; RT = response time; AI = anterior insula; TPJ = temporoparietal junction; rsFC = resting state functional connectivity; ACC = anterior cingulate cortex. † indicates essential predictors exceed the average absolute coefficient of all retained variables (.054).

C. Elastic net regressions predicting Post-treatment PHQ-9 scores using only participants with complete data (i.e., with no imputation of missing data)

37 participants had complete data on all variables.

Stage 1: Cognitive control performance as a predictor of symptom change during iCBT.

We entered basic demographic/treatment variables, including age, gender, treatment group, and baseline PHQ-9 score into the model, along with Flanker performance variables including Flanker accuracy, Flanker RT, Gratton accuracy, Gratton RT, post-error accuracy, and post-error RT. Essential variables retained in the final model included demographic/treatment variables (treatment group and gender) and the interactions between treatment group and: Gratton accuracy and post-error accuracy. Given the lower number of participants, we used a threshold of 5000/10000 replicates for variable retention. See Supplementary Table S8.

Stage 2: Resting state functional connectivity in cognitive/emotional control network regions as a predictor of symptom change during iCBT.

We entered basic demographic/treatment variables, including age, gender, treatment group, and baseline PHQ-9 score into the model, along with connectivity values among dACC, left AI, right AI, and TPJ (Figure 1) ROIs. Essential variables retained in the final model included demographic/treatment variables (treatment group and gender). See Supplementary Table S8.

Stage 3: Cognitive control performance and rsFC in cognitive/emotional control network regions as predictors of symptom change during iCBT.

We entered baseline PHQ-9 scores into the model, along with variables retained at Step 1 and Step 2, including treatment group, gender, Baseline PHQ-9, Flanker accuracy, Flanker RT, Gratton RT, Gratton accuracy, Post-error RT, and right AI – TPJ rsFC. Essential variables retained in the final model included demographic/treatment variables and the interactions between treatment group and Gratton accuracy and post-error accuracy. See Supplementary Table S8.

Supplementary Table S8

Variable	**Proportion of replicates with non-zero coefficients**	**Average Coefficient**
Stage 1		
Tx group (MDD)†	1	-0.273
Baseline PHQ-9	0.6465	0.027
Gender†	1	0.34

Flanker RT	1	0.068
Gratton accuracy	0.6283	0.038
Gratton RT	0.9948	-0.07
Post-error RT	0.7481	-0.047
Tx group (MDD) * Baseline PHQ-9	0.5265	0.039
Tx group (MDD) * Age	0.6647	0.045
Tx group (MDD) * Flanker accuracy	0.6041	-0.046
Tx group (MDD) * Flanker RT	0.6887	0.048
Tx group (MDD) * Gratton accuracy†	1	-0.234
Tx group (MDD) * Gratton RT	0.6299	-0.095
Tx group (MDD) * Post-error accuracy†	1	0.183
Tx group (MDD) * Post-error RT	0.6457	0.066
Stage 2		
Tx group (MDD)†	1	-0.32
Gender†	1	0.272
Right AI-TPJ rsFC	0.9981	0.057
Stage 3		
Tx group (MDD)†	1	-0.239
Baseline PHQ-9	0.9397	0.037
Gender†	1	0.272
Flanker RT	0.999	0.063
Gratton accuracy	0.6836	0.015
Gratton RT	0.9968	-0.052
Post-error RT	0.959	-0.04
Right AI-TPJ rsFC	0.9993	0.074
Tx group (MDD) * Baseline PHQ-9	0.8199	0.042
Tx group (MAC) * Age	0.6751	-0.008
Tx group (MDD) * Age	0.9099	0.045
Tx group (MAC) * Flanker accuracy	0.6706	-0.004
Tx group (MDD) * Flanker accuracy	0.8525	-0.043
Tx group (MDD) * Flanker RT	0.917	0.047
Tx group (MDD) * Gratton accuracy†	0.9987	-0.199
Tx group (MDD) * Gratton RT	0.888	-0.074
Tx group (MAC) * Post-error accuracy	0.9912	-0.057

Tx group (MDD) * Post-error accuracy†	0.9997	0.136
Tx group (MDD) * Post-error RT	0.8698	0.052

Note. Tx = treatment; RT = response time; AI = anterior insula; TPJ = temporoparietal junction; rsFC = resting state functional connectivity.

Variables in ***bold italics*** are significant in models of both imputed and non-imputed data. † indicates essential predictors exceed the average absolute coefficient of all retained variables (Step 1: .104, Step 2: .172, Step 3: .076).

D. *Variables associated with baseline depression*

We applied a three-stage approach similar to that for the prediction of post-treatment PHQ-9 scores. In Stage 1, we entered age, gender, and the Flanker behavioral variables as predictors of baseline PHQ-9 scores. We used a cutoff of 7500 replicates, as in the primary analyses. Essential variables retained in the final model included treatment group, Post-error RT and the interaction between treatment group and Post-error RT. In Stage 2, we entered age, gender, and the rsFC variables as predictors of baseline PHQ-9 scores. No variables (besides the intercept) were retained in the final model. In Stage 3, we entered variables retained at Stage 1, including treatment group, Flanker RT, Gratton RT, post-error accuracy, and post-error RT. Essential variables retained in the final model included treatment group, post-error accuracy, post-error RT, and the interactions between treatment group and: Flanker RT and post-error RT. See Supplementary Table S9.

Supplementary Table S9

Variable	**Proportion of replicates with non-zero coefficients**	**Average Coefficient**
Stage 1		
Tx group (MDD)†	0.9676	-0.196
Gratton RT	0.9603	-0.045
Post-error accuracy	0.9613	0.154
Post-error RT†	0.9691	-0.307
Tx group (MDD) * Flanker RT	0.8675	-0.083
Tx group (MDD) * Post-error accuracy	0.9691	0.108
Tx group (MDD) * Post-error RT†	0.9566	0.309
Stage 2		
N/A		
Stage 3		
Tx group (MDD)†	1	-0.256
Gratton RT	1	-0.06
Post-error accuracy†	1	0.273

Post-error RT†	1	-0.509
Tx group (MAC) * Flanker RT†	1	0.284
Tx group (MDD) * Flanker RT	1	-0.088
Tx group (MDD) * Post-error accuracy	1	0.061
Tx group (MDD) * Post-error RT†	1	0.585

Note. Tx = treatment; RT = response time. † indicates essential predictors exceed the average absolute coefficient of all retained variables (Step 1: .16, Step 2: N/A, Step 3: .248).

E. Entering all variables simultaneously into the elastic net as a single step, using HAMD scores instead of PHQ-9 scores

In response to an inquiry regarding our use of PHQ-9 scores instead of HAMD scores, we repeated the main analysis using HAMD scores. We entered all variables into the model in a single stage (as in A above). Given the large number of entered variables, we used a lower cutoff (5000 out of 10,000 replicates) to consider a variable retained. We entered basic demographic/treatment variables, including age, gender, treatment group, and baseline HAMD score into the model, along with Flanker performance variables including Flanker accuracy, Flanker RT, Gratton accuracy, Gratton RT, post-error accuracy, and post-error RT; and connectivity values among dACC, left AI, right AI, and TPJ ROIs (n = 32 variables, including interactions and the intercept).

See Supplement section A above for results obtained using the PHQ-9 and Supplementary Table S10 for results obtained using the HAMD. Treatment group and Flanker RT were retained as essential predictors in the model regardless of whether PHQ-9 or HAMD was used as the measure of depression. Right AI-left AI rsFC, and the interactions between treatment group and: age and right AI-left AI rsFC were retained in both the PHQ-9 and HAMD models but did not exceed the average absolute coefficient of all retained variables in the HAMD model. Findings related to Gratton and post-error accuracy and right AI-TPJ connectivity were specific to the PHQ-9 analysis. This may be related to clinically relevant differences between PHQ-9 (self-report) and HAMD (clinician report), see e.g. [12,13]. Since use of HAMD is unlikely to persist in clinical practice of iCBT given that it is not self-administered, we opted to focus the bulk of the paper on prediction of reduction in PHQ-9 scores (e.g. [14]).

Supplementary Table S10

Variable	**Proportion of replicates with non-zero coefficients**	**Average Coefficient**
Tx group (MDD)†	1	-0.427
Age	1	0.046
Flanker RT†	1	0.228
Right AI-Left AI rsFC	0.9971	-0.034

Tx group (MDD) * Age	0.9694	0.016
Tx group (MDD) * Right AI-Left AI rsFC	1	-0.162

Note. Tx = treatment; RT = response time; AI = anterior insula; rsFC = resting state functional connectivity. † indicates essential predictors exceed the average absolute coefficient of all retained variables (.165).

F. Entering all variables simultaneously into a binomial logistic elastic net as a single step, using response status instead of PHQ-9 scores

In response to an anonymous reviewer regarding our use of continuous PHQ-9 scores instead of response status, we repeated the analysis using response status defined as a ≥50% decrease in PHQ-9 scores. We entered all variables into the model in a single stage (as in A above). Given the large number of variables, we used a lower cutoff (5000 out of 10,000 replicates) to consider a variable retained. We entered basic demographic/treatment variables, including age, gender, treatment group, and baseline PHQ-9 score, into the model, along with Flanker performance variables including Flanker accuracy, Flanker RT, Gratton accuracy, Gratton RT, post-error accuracy, and post-error RT; and connectivity values among dACC, left AI, right AI, and TPJ ROIs (n = 32 variables, including interactions and the intercept).

See Supplement section A above for results obtained using the continuous PHQ-9 scores and Supplementary Table S11 for results obtained using response status.

When comparing the single step model predicting response status with the stage 3 model predicting continuous post-treatment PHQ-9 scores, the interactions between treatment group and: Flanker RT and Gratton accuracy were retained as essential predictors in the model regardless of whether continuous post-treatment PHQ-9 scores or response status were used as the measure of treatment outcome. Flanker RT, Right AI-TPJ rsFC, Right AI-left AI rsFC, and the interactions between treatment group and age were retained in both the continuous post-treatment PHQ-9 scores and response status models but did not exceed the average absolute coefficient of all retained variables in the response status model. Although the interaction between treatment group and baseline PHQ-9 scores were retained in both models, the direction of associations was opposite. Findings related to the left AI-TPJ and the interaction between treatment group and dACC-right AI rsFC were specific to the response status model. The interactions between treatment group and: post-error accuracy, right AI-TPJ rsFC and right AI-left AI rsFC were retained as essential predictors in Stage 3 of the model predicting continuous post-treatment PHQ-9 scores. All variables in the response status model were retained in the single step model predicting continuous post-treatment PHQ-9 scores (the interaction between treatment group and baseline PHQ-9 and dACC-right AI rsFC showed opposite patterns in both models, however). Overall, the model predicting response status showed similar results to the model predicting continuous PHQ-9 scores. Differences in findings may be due to lower variance in the binary response status variable compared to the continuous PHQ-9 score.

Supplementary Table S11

Variable	**Proportion of replicates with**	**Average Coefficient**

	non-zero coefficients	
Flanker RT	**1**	**-0.317**
Left AI-TPJ rsFC	0.9965	0.192
Right AI-TPJ rsFC	**1**	**-0.424**
Right AI-Left AI rsFC†	**1**	**0.503**
Tx group (MDD) * Baseline PHQ-9⁺	**0.9713**	**0.121**
Tx group (MDD) * Age	**1**	**-0.122**
Tx group (MDD) * Flanker RT†	**1**	**-0.917**
Tx group (MDD) * Gratton accuracy†	**1**	**1.09**
Tx group (MDD) * dACC-right AI rsFC	0.6271	-0.062

Note. Tx = treatment; RT = response time; AI = anterior insula; rsFC = resting state functional connectivity. † indicates essential predictors exceed the average absolute coefficient of all retained variables (.449). ⁺ indicates predictors that show the opposite direction compared to the model predicting continuous PHQ-9 scores

Variables in ***bold italics*** are significant in the Stage 3 model with continuous post-treatment PHQ-9 scores and the one-stage response status.

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