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ARTICLE

Rostral anterior cingulate network effective connectivity in depressed adolescents and associations with treatment response in a randomized controlled trial

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The rostral anterior cingulate cortex (rACC) is consistently implicated in the neurobiology of depression. While the functional connectivity of the rACC has been previously associated with treatment response, there is a paucity of work investigating the specific directional interactions underpinning these associations. We compared the fMRI resting-state effective connectivity of 94 young people with major depressive disorder and 91 healthy controls. Following the fMRI scan, patients were randomized to receive cognitive behavioral therapy for 12 weeks, plus either fluoxetine or a placebo. Using spectral dynamic causal modelling, we examined the effective connectivity of the rACC with eight other regions implicated in depression: the left and right anterior insular cortex (AIC), amygdalae, and dorsolateral prefrontal cortex (dlPFC); and in the midline, the subgenual (sgACC) and dorsal anterior cingulate cortex (dACC). Parametric empirical Bayes was used to compare baseline differences between controls and patients and responders and non-responders to treatment. Depressed patients demonstrated greater inhibitory connectivity from the rACC to the dlPFC, AIC, dACC and left amygdala. Moreover, treatment responders illustrated greater inhibitory connectivity from the rACC to dACC, greater excitatory connectivity from the dACC to sgACC and reduced inhibitory connectivity from the sgACC to amygdalae at baseline. The inhibitory hyperconnectivity of the rACC in depressed patients aligns with hypotheses concerning the dominance of the default mode network over other intrinsic brain networks. Surprisingly, treatment responders did not demonstrate connectivity which was more similar to healthy controls, but rather distinct alterations that may have predicated their enhanced treatment response.

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders, with an estimated prevalence of 10% within the adult population [1]. Despite several psychotherapeutic and pharmacological interventions, overall remission rates remain below 50% [2–4]. Adolescence is the peak period of depression onset [5], with those experiencing depression at this stage often showing poor response to typical treatments [6]. This is likely in part due to the reduced relative effectiveness of antidepressant medication for this population [7, 8], which may result from an increased responsivity to placebos [9, 10]. However, much of the rationale for explaining variability in treatment response remains speculative due to our limited understanding of the neurobiological mechanisms of depression [11]. As such, recent neuroimaging work has attempted to identify brain characteristics that contribute to diagnostic and prognostic outcomes: so-called *neural biomarkers* [12–14].

Widespread interactions both between and within intrinsic brain networks have previously been associated with the manifestation of depressive symptoms [11, 15], with the default mode (DMN), salience, and central executive networks (CEN) all being implicated in MDD [16, 17]. As part of the DMN, the rostral anterior cingulate cortex (rACC) is one of the more consistently identified regions implicated in depression treatment response [18–20]. In healthy individuals, the rACC and wider DMN are highly active during rest and self-referential processing [21, 22] and are suppressed by tasks that demand an external focus [23, 24]. Due to their opposing relationship with attentional demands, the DMN is commonly shown to be anticorrelated with both the dorsal attentional network and CEN in healthy individuals [25, 26]. Patients with depression demonstrate elevated levels of activity in rACC at rest [27–29] and reduced suppression during external tasks [30]. MDD patients also exhibit altered rACC connectivity, illustrating increased connectivity from the dorsal anterior cingulate cortex (dACC) to rACC [31] and decreased (or more negative) connectivity between the DMN and CEN [32, 33]. Moreover, depressive symptom severity has been negatively associated with functional connectivity between the rACC and dorsolateral prefrontal cortex [dlPFC; 34].

The rACC has also been shown to predict treatment response and remission [29, 35]. Specifically, higher pretreatment activity of

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rACC at rest has been associated with treatment response [18, 36], which has been hypothesized to reflect a more adaptive form of self-referential processing [29]. Interactions between the rACC and other regions, including the anterior insular cortex (AIC), have also been positively associated with greater depressive symptom improvements [37, 38]. Furthermore, connectivity between the ventromedial prefrontal cortex/rACC and subgenual anterior cingulate cortex [sgACC; 35, 39], dlPFC [40, 41] and amygdala [42] have all been associated with poorer treatment outcomes. Psychiatric disorders including post-traumatic stress disorder, have also been previously associated with a pattern of predominate bottom-up connectivity from the amygdala to sgACC [43]. This has been hypothesized to be due emotional dysregulation, with neurofeedback training being associated with increased bidirectional connectivity between the prefrontal and amygdala [44]. Together these results suggest that these extended rACC network interactions appear to influence depression severity and response trajectory. While directional (causal) connectivity within the DMN has previously been associated with treatment response [45], the directional influences from other aforementioned regions and their effect on treatment response remain unclear.

This study aimed to thoroughly examine rACC network interactions in young people with depression and their associations with treatment response. We used spectral dynamic causal modelling [DCM; 46, 47] to examine baseline resting-state effective connectivity of rACC with the bilateral amygdalae, AIC, dlPFC, as well as sgACC and dACC. By investigating these parameters in a cohort of young people with depression who participated in a randomized controlled trial (Youth Depression Alleviation [YoDA-C]) [48], we also aimed to characterize how these baseline alterations predicted response to treatment. Our first hypothesis was that depression would be characterized by greater inhibitory connectivity from the rACC to bilateral dlPFC. Our second hypothesis, which was broadly motivated by previous research but was also exploratory in nature, was that treatment responders would demonstrate greater excitatory connectivity from the rACC to AIC [37, 38] and greater negative connectivity from the rACC to dlPFC [40, 41], sgACC [35, 39] and amygdala [42] in comparison with non-responders at baseline.

METHODS

Participants

One hundred and eleven unmedicated, help-seeking depressed participants, aged between 15 to 25 years, were recruited through specialist mental health clinics located in the northern and western suburbs of Melbourne, Australia. Participants were enrolled as part of the YoDA-C trial (for full details see [48]). In brief, YoDA-C was a randomized, double-blind, placebo-controlled, multicenter clinical trial comparing the efficacy of 12 weeks of cognitive behavioral therapy (CBT), plus either fluoxetine or a placebo. These patients had been diagnosed with MDD, as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID; 49]. Depressive symptoms were at least of a moderate level of severity, as indicated by a Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥20. In addition, these participants had no lifetime or current diagnosis of a psychotic or bipolar disorder, no current treatment with antidepressant medication, were not pregnant, and had an estimated IQ >85 as determined by the Wechsler Test of Adult Reading [50]. Response from depression was defined as a MADRS symptom score reduction of 50% or greater following 12 weeks of treatment [51]. This study also recruited 104 age and sex-matched healthy participants through online advertisements. They had no past mental health disorder diagnoses as assessed through the SCID criteria or an IQ lower than 85.

All participants were provided with, and signed, an informed consent form to participate in the study. For those under the age of 18, both the consent of the participant and a parent were required. This study and consent process had been approved by the Melbourne Health Human Research and Ethics Committee. Of the total number of participants who underwent scanning a total of 13 controls and 17 patients were omitted from further analyses. This was due to incidental findings (four controls, one patient), the lack of follow-up MADRS data (eight patients) and not having sufficient activation in at least one region to undergo DCM analysis (nine controls, eight patients; see below). As a result, 91 healthy controls and 94 MDD participants were included in our analyses. Of these 94 MDD participants, 44 were shown to respond following treatment, while 50 were observed to be treatment non-responders (see Fig. S1 for CONSORT flow diagram).

Image acquisition

A 3T General Electric Signa Excite system with an eight-channel phased-array head coil was used in combination with ASSET parallel imaging. The functional sequence consisted of a single shot gradient-recalled echo-planar imaging sequence in the steady state (repetition time, 2000 ms; echo time, 35 ms; and pulse angle, 90°) in a 23 cm field-of-view, with a 64 × 64-pixel matrix and a slice thickness of 3.5 mm (no gap). Thirty-six interleaved slices were acquired parallel to the anterior-posterior commissure line with a 20° anterior tilt to better cover ventral prefrontal brain regions. The total sequence duration was 8 minutes, corresponding to 240 whole-brain echo-planar imaging volumes. Participants were instructed to keep their eyes closed for the duration of the scan. The first four volumes from each run were automatically discarded to allow for signal equilibration. A T1-weighted high-resolution anatomical image was acquired for each participant to assist with functional timeseries co-registration (140 contiguous slices; repetition time, 7.9 s; echo time, 3 s; flip angle, 13°; in a 25.6 cm field-of-view, with a 256 × 256-pixel matrix and a slice thickness of 1 mm). To assist with noise reduction and head immobility, all participants used earplugs and had their heads supported with foam-padding inserts.

Image analysis and preprocessing

All analyses were conducted using the Spartan High Performance Computer hosted at The University of Melbourne [52]. Preprocessing occurred through the use of ENIGMA HALFpipe Version 1.0.0 [53], a semi-automated pipeline based on fMRIprep [54]. A high-pass filter (125 s) was used to account for low-frequency noise and smoothing occurred with a 6 mm full-width at half-maximum kernel. Grand mean scaling was deployed with a mean of 10,000 and ICA-AROMA was used to regress out motion artefacts [55].

Dynamic causal modelling overview

DCM is a technique that estimates the directed functional interactions between neural populations from neuroimaging data [56, 57]. In contrast to stochastic DCM, spectral DCM is more computationally efficient and thus is more suitable for examining interactions between a relatively large number of regions [46, 58]. Connectivity between regions of interest is measured in hertz (Hz), with positive values being indicative of putative excitation between regions while negative values represent putative inhibition. Conversely, self (or recurrent) connections are inhibitory and are log-scaled such that positive values represent greater inhibition while negative values indicate reduced inhibition.

Timeseries extraction, model specification and estimation

DCM analysis was conducted in MATLAB Version 9.8 (The MathWorks Inc., Natick, USA) and Statistical Parametric Mapping (SPM) Version 12- v7771 (Wellcome Trust Centre for Neuroimaging, London, UK). Our chosen volumes of interest (VOIs) were informed by reviews investigating predictors of treatment response [16, 29] and included bilateral AIC, dlPFC, and amygdalae, as well as the rACC, sgACC, and dACC. The Montreal Neurological Institute coordinates for these regions were identified using previously reported peak coordinates from meta-analyses and large-scale functional connectivity studies. The precise coordinates were as follows: amygdalae [±22, −6, −12] [59], AIC [36, 16, 4; −35, 14, 5] [60], dlPFC [±30, 43, 23] [61], rACC [−2,3,39] [62], dACC [4,30,30] [63], and sgACC [−8,2,18] [64]. For visualization of region locations see Fig. S2. The timeseries from these VOIs were extracted using the principal eigenvariate of all voxels in a sphere within a radius of 6 mm of the centroids for midline regions (rACC, sgACC, dACC) and 4 mm for lateralized regions (amygdalae, AIC and dlPFC) and which were present at a threshold of $p < 0.05$, uncorrected at an individual (subject) level [65].

The candidate model space was specified and estimated with DCM12.5. The parent model contained connections between all regions, except for connections between non-analogous contralateral regions (e.g., no connection between the right amygdala and left dlPFC).

Parametric empirical bayes

We used Parametric Empirical Bayes (PEB) to examine between-group effects on within-subjects' parameters [66]. PEB allows for the inclusion of estimated variance (in addition to the estimated means) of each parameter when investigating between-group effects, unlike comparison using classical tests which only use estimated mean values. The posterior probability (PP) was calculated using the free energy (with vs. without) option, which compares the evidence for all models in which a particular parameter is switched on with the evidence for models in which it is switched off. A very conservative threshold of PP >0.99 was used to include only those parameters which had a very strong amount of evidence [67]. Consistent with our previous work [68], we constructed a second level PEB model which included six regressors. The first regressor represents the mean connectivity across all participants, to which the between-subject effects add to or subtract from. The next two of these regressors were of primary interest in this paper: differences between healthy controls and MDD patients and baseline differences between patients who went on to respond to treatment and those who did not. The covariates included in this model were: differences at baseline between treatment groups, the interaction of response and treatment type, and the effect of age.

Having estimated a group-level PEB model, we then searched over nested PEB models, pruning parameters that did not contribute to overall model evidence [57, 69]. Bayesian model averaging was performed on these models after the final iteration to determine the strength of connections in the last Occam's window of 256 models. We repeated this analysis with response replaced with remission (defined as MADRS ≤ 7) in order to highlight those parameters that were associated with treatment response and that were sufficiently robust to also demonstrate a meaningful effect for remission.

Leave-one-out cross-validation

While PEB provides a hierarchical method for assessing connectivity differences between groups, it does not provide an assessment of the predictive validity of these parameters. This can be measured through the use of leave-one-out cross-validation (LOOCV) in the PEB framework. While concerns have been raised about the use cross-validation for group comparison [70], particularly in relation to its tendency to overfit and result in inconsistent model estimates, this is not the aim of cross-validation in PEB. Rather than examining differences between groups, LOOCV (as implemented in SPM as the *spm.dcm_loo.m* function) aims to determine whether the size of the effect on a set of parameters is sufficiently large to predict group allocation [67]. This does so by estimating a group-level PEB model while excluding one subject and using this PEB model to predict whether the left-out subject would be a treatment responder or non-responder, based on the included parameters (in this case those that demonstrated differences between treatment responders and non-responders). This predicted response status can then be correlated with the observed response status (whether they responded to treatment or not as part of the trial) to determine the accuracy of this prediction. A significant correlation between the expected and observed values demonstrates that the effect size estimated by was sufficiently large to predict whether left-out subjects' was a responder or a non-responder above chance (see [67] for further details). Thus, for cases in which differences are known to occur, LOOCV assess whether the size of the effect is large enough to provide predictive utility.

RESULTS

Demographic and clinical results

As expected, patients' MADRS symptoms were significantly greater than controls at baseline ($t(142.16) = -49.14$, $p < 0.001$; Table 1). Treatment response rates were similar for both treatment arms (CBT and placebo = 45%; CBT and fluoxetine = 48%). Consistent with the full trial analysis [48], no clinical or demographic differences were observed between treatment responders and non-responders at baseline (Table 2). No clinical or demographic differences were observed between the two treatment arms (Table S1).

Differences in effective connectivity between depressed patients and controls

Depressed patients demonstrated strong evidence for greater inhibitory connectivity from the rACC to the left amygdala (expected value = −0.06 Hz), right AIC (expected value = −0.13 Hz), left AIC (expected value = −0.13 Hz), and left dlPFC (expected value = −0.10 Hz). Reduced inhibitory connectivity was shown from the left amygdala to left AIC (expected value = 0.08 Hz). Reduced excitatory connectivity was observed from the right AIC to right dlPFC (expected value = −0.06 Hz), right AIC to left AIC (expected value = −0.07 Hz) and right dlPFC to sgACC (expected value = −0.04 Hz). See Fig. 1 and Table 3 for depiction of connectivity differences between healthy controls and MDD patients.

Differences in effective connectivity between treatment responders and non-responders

In comparison to non-responders, treatment responders demonstrated greater baseline inhibitory connectivity from the rACC to dACC (expected value = −0.18 Hz). Treatment responders showed reduced inhibition from the sgACC to both the right (expected value = 0.12 Hz) and left amygdala (expected value = 0.09 Hz). Responders also illustrated greater excitatory connectivity was demonstrated from the dACC to sgACC (expected value = 0.06 Hz) and reduced excitatory connectivity was shown from the left AIC to left dlPFC (expected value = −0.08 Hz) and right AIC to right dlPFC (expected value = −0.07 Hz). See Fig. 2 and Table 3 for depiction of all difference between treatment responders and non-responders at baseline. The expected values and PP for all between-group effects are reported in Supplementary Table S2 (Response) and Supplementary Table S3 (Remission).

Leave-one-out cross-validation

Using those parameters which demonstrated differences between responders and non-responders we performed a LOOCV to determine whether the overall size of this effect on these parameters could significantly predict the treatment response status. Examination of all MDD patients resulted in an out-of-

Table 1. Characteristics of healthy controls and major depressive disorder patients.

Characteristics	Healthy controls ($N = 90$) Mean or *N*	SD or Percentage	MDD ($N = 94$) Mean or *N*	SD or Percentage	Cohen's *d* or Cramer's V	*p*
Age (years)	20.11	2.7	19.73	2.8	0.14	0.353
Baseline MADRS	2.13	2.8	32.77	5.3	−0.7.22	<0.001
Female	49	53.8	59	62.7	0.09	0.219
Ethnicity					0.23	0.085
Caucasian	65	72.2	83	88.3		
Black or African	1	1.1	1	1.1		
Asian	19	21.1	9	9.6		
South American	3	3.3	0	0		
Indian	1	1.1	0	0		
Middle Eastern	1	1.1	1	1.1		

Table 2. Characteristics of treatment responders and non-responders.

	Non-responders ($N = 50$)		Responders ($N = 44$)			
Characteristics	**Mean or Median**	**SD or Q1–Q3**	**Mean or Median**	**SD or Q1–Q3**	**Cohen's *d***	***p***
Age (years)	19.97	2.8	19.45	2.7	0.19	0.468
Age of Onset	15.01	3.0	15.81	2.3	0.30	0.346
Baseline MADRS	33.50	5.4	31.93	5.2	0.30	0.346
Baseline GAD7	14.14	5.4	12.77	5.8	0.26	0.397
Baseline SOFAS	57.09	12.7	59.0	9.7	−0.17	0.418
No. of therapy sessions	7.04	2.7	6.02	2.5	0.38	0.303
No. of episodes	3	1–11	2	1–4	0.18	0.468
Characteristics	***N***	**Percentage**	***N***	**Percentage**	**Cramer's V**	***p***
Female	33	66.0	26	59.1	0.07	0.543
Comorbid Anxiety Disorder	35	70.0	22	50.0	0.20	0.303
Comorbid Substance Use	9	18.0	6	13.6	0.06	0.564
Ethnicity					0.20	0.303
Caucasian	48	96.0	35	79.5		
Black or African	0	0	1	2.3		
Asian	2	4.0	7	15.9		
South American	0	0	0	0		
Indian	0	0	0	0		
Middle Eastern	0	0	1	2.3		

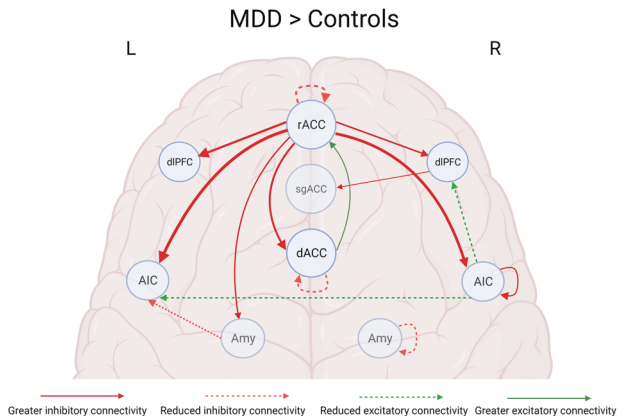

Fig. 1 Differences in effective connectivity between major depressive disorder patients and healthy controls. Arrows have been weighted to indicate the relative size of the effects. Image created with BioRender (www.biorender.com).

samples correlation between the predicted and observed response status of $r = 0.33$, $p < 0.001$ (Fig. 3A). We then examined whether the accuracy of this prediction differed between the two treatment arms. Subsequent analyses for these groups separately revealed a correlation of $r = 0.12$, $p = 0.195$ for the CBT and fluoxetine group (Fig. 3B) and $r = 0.48$, $p < 0.001$ for the CBT and placebo group (Fig. 3C). This indicated that while these parameters could be used to significantly predict treatment response status across all MDD participants above chance, the accuracy of this effect was largely driven by those in the CBT and placebo group.

DISCUSSION

This study examined alterations in resting-state effective connectivity and their associations with treatment response in young people with depression. We demonstrated greater inhibitory connectivity from the rACC to bilateral dlPFC in depressed patients, which supported our first hypothesis. Notably, this inhibitory hyperconnectivity was more widespread than hypothesized, also occurring from rACC to bilateral AIC, dACC and right amygdala. In contrast to our second hypothesis, treatment responders demonstrated greater inhibitory connectivity from rACC to dACC at baseline. Moreover, we demonstrated that a subset of these parameters that were significant predictors of treatment response, and of note, prediction was particularly strong for those treated with combined treatment with CBT and a placebo. These findings support the central role of the rACC in depressive symptom and course, particularly in terms of its interactions with other cingulate regions.

Differences in effective connectivity between depressed patients and controls

Depressed participants showed a pattern of greater inhibitory connectivity from the rACC to the majority of other regions under examination. While this is generally consistent with recent work, these effects also appear more excessive than hypothesized. The anticorrelations between the anterior DMN and CEN have been previously shown to be largely driven by activity of the DMN [71]. In depressed patients, both the rACC and the wider DMN demonstrate elevated levels of activity at rest when compared with healthy controls [27–29]. Our results expand upon these findings to illustrate greater specificity in terms of the directionality and magnitude of these connectivity alterations. They suggest that the reductions in functional connectivity between DMN to CEN likely result from greater inhibitory connectivity originating from the DMN, and in particular the rACC [32]. This dominance of the DMN over the CEN in depression is also highlighted in the work of Hamilton et al. [72], who reported that the level of DMN dominance was positively correlated with maladaptive rumination. As such, the greater negative connectivity of the anterior DMN over the CEN may represent an altered ability to switch from internal mental processes to attend to external task-relevant stimuli thereby contributing to the manifestation of these symptoms [73, 74].

While not specifically hypothesized, alterations from the rACC to AIC, dACC and left amygdala were also observed in our sample. These findings and the altered connectivity from the rACC to bilateral dlPFC are consistent with the changes to

Table 3. Summary of connectivity differences between major depressive disorder patients and healthy controls as well as between treatment responders and non-responders.

	Parameter estimates (Hz)
MDD > Healthy Controls	
R_Amygdala → R_Amygdala	−.07
L_Amygdala → L_AIC	.08
R_AIC → R_AIC	.06
R_AIC → L_AIC	−.07
R_AIC → R_dlPFC	−.06
rACC → L_Amygdala	−.07
rACC → R_ AIC	−.14
rACC → L_AIC	−.15
rACC → rACC	−.10
rACC → dACC	−.10
rACC → R_dlPFC	−.08
rACC → L_dlPFC	−.12
dACC → rACC	.05
dACC → dACC	−.08
R_dlPFC→sgACC	−.04
Responders > Non-Responders	
L_Amygdala → dACC	−.17
R_AIC → R_dlPFC	−.07
L_AIC → L_dlPFC	−.08
sgACC → R_Amygdala	.12
sgACC → L_Amygdala	.09
rACC → dACC	−.18
dACC → sgACC	.06

AIC anterior insular cortex, *dACC* dorsal anterior cingulate cortex, *dlPFC* dorsolateral prefrontal cortex, *MDD* major depressive disorder, *rACC* rostral anterior cingulate cortex, *sgACC* subgenual anterior cingulate cortex.
Note. All parameters shown demonstrated a posterior probability > .99.

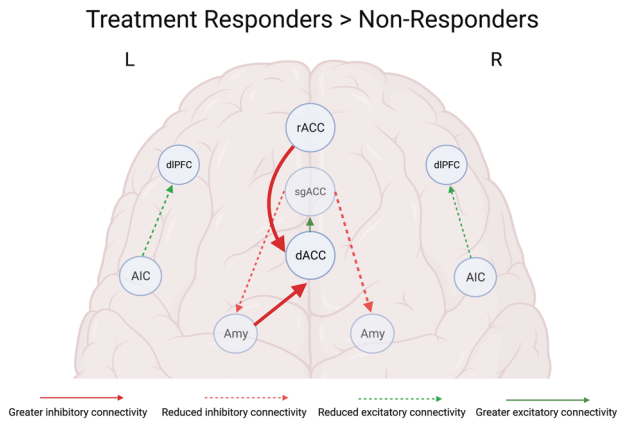

Fig. 2 Differences in effective connectivity between treatment responders and non-responders at baseline. Arrows have been weighted to indicate the relative size of the effect. Image created with BioRender (www.biorender.com).

intrinsic networks postulated in the triple network model of psychopathology [75]. This model hypothesizes that different psychiatric disorders are underpinned by abnormal interactions between the DMN, salience network and CEN. Within this framework, depression is viewed as a disorder marked primarily by DMN dysfunction (abnormal self-referential processing and rumination) with additional alterations in the salience network (abnormal processing of negative stimuli) [76]. The AIC and dACC are canonically part of the salience network [77, 78], while the amygdala is also implicated in the processing of salience information [79]. The salience network, particularly the AIC, also plays an important role in mediating dynamic interactions between the DMN and CEN and in the assignment of saliency to both internal events and external stimuli [77]. These results indicate that the altered switching between the DMN and CEN previously associated with depression appears to occur both directly, through greater inhibition of the CEN, and indirectly, through greater inhibition of the salience network. In addition, we observed reduced connectivity from the AIC to dlPFC, which is consistent with other research examining between-network resting-state effective connectivity [80, 81]. This has been hypothesized to broadly relate to depression associated abnormalities in attention and decision-making processes [80]. Our finding builds upon this work by illustrating that responders also have reduced connectivity when compared with non-responders. This suggests that this reduced AIC to dlPFC connectivity may be indicative of a more prototypical depression, which responds better to common antidepressant treatment.

Differences in effective connectivity between treatment responders and non-responders

Of the connections originating from the rACC, only connectivity from the rACC to dACC was different at baseline between responders and non-responders. Notably, the directionality of this effect was the same for the associations with both depression and treatment response. As previously highlighted, the dysfunctional interaction between the DMN and salience network may represent interference with the dynamic switching of salience attribution between internal and external stimuli by maladaptive ruminative processes [77, 82]. As CBT aims to support individuals in overcoming rigid thought patterns [83], this dysfunctional over-suppression of the salience network may be particularly receptive to treatments that focus on disrupting this process. Thus, this inhibitory hyperconnectivity observed in depressed patients may predicate or enhance treatment response, specifically for those treated with CBT and a placebo. The LOOCV results further reinforces that this effect may be particularly useful in predicting response for those treated in this manner. Our previous work in this sample demonstrated that greater excitation from the amygdala to dlPFC during sad expression processing and reduced excitation from the amygdala during fearful expression processing at baseline in responders compared with non-responders [68]. Despite identifying different connectivity parameters, this overall preferential predictive effect for those treated with CBT and a placebo is consistent with our prior work [68] and appears to suggest that, more generally, connectivity alterations are more predictive for those given this treatment. As these results were identified in the same participant sample, replication in other samples would further aid in supporting these conclusions. Nevertheless, these differences may be indicative of general prognostic factors, or unique predictors for CBT treatment, which are enhanced in the absence of pharmacological interventions. The antidepressant effects of selective serotonin reuptake inhibitors, such as fluoxetine, are hypothesized to occur through the increasing of neuroplasticity [84]. This in turn may alter connectivity variability in such a way that its initial state becomes less informative of future response. Thus, despite these parameters being predictive of overall response, their specific utility for those treated with CBT and placebo likely occurs not as a result of the treatment itself, but because of the lack of fluoxetine in this treatment arm. The ultimate scope and clinical utility of such findings is dependent on two features that remain unclear. First, whether the effects observed here are truly predictive response to CBT or simply generally prognostic, and second, whether the

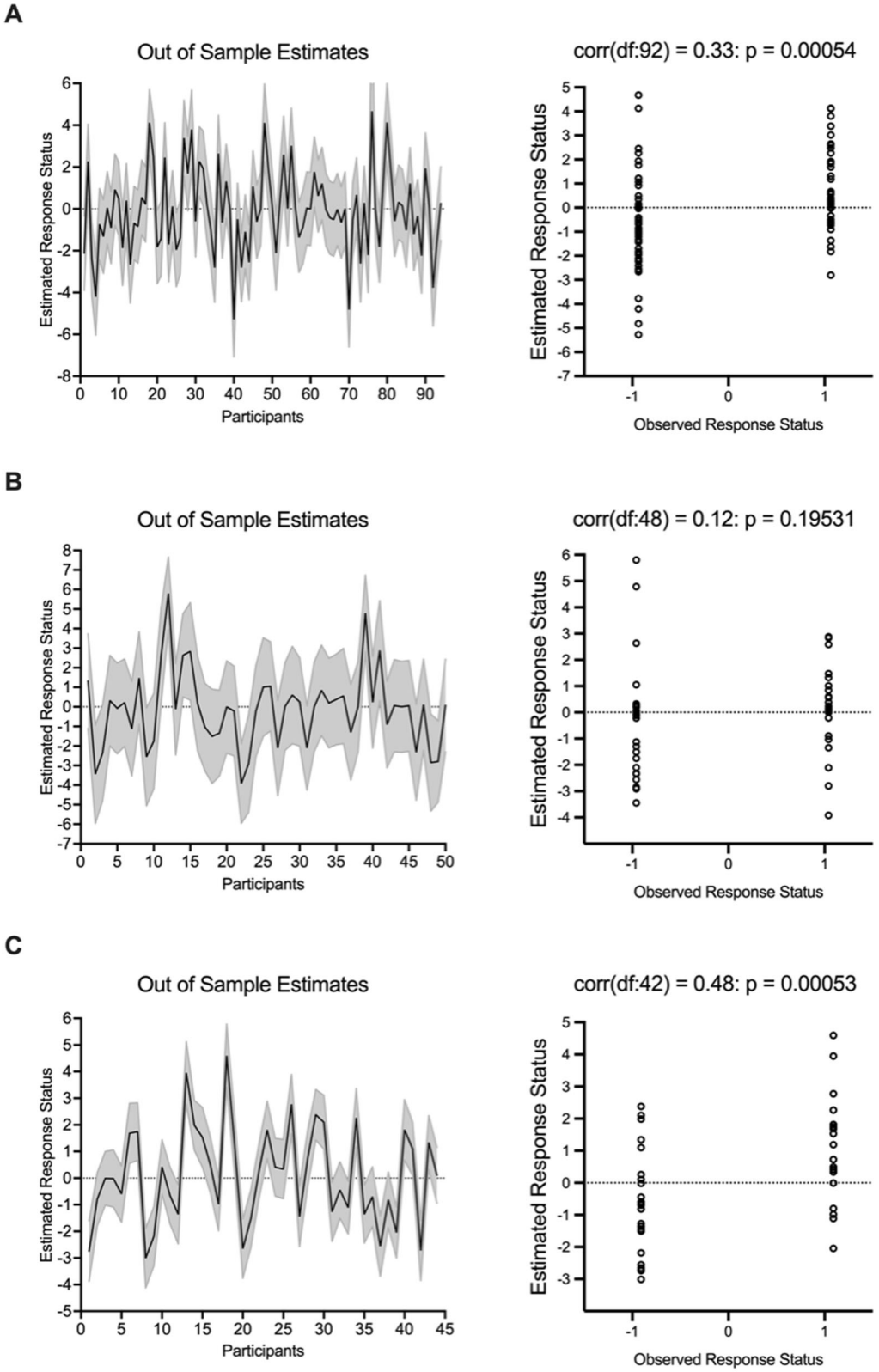

Fig. 3 Leave-one-out cross-validation predicting response following treatment for depressed patients. *Left:* The out-of-samples estimated of the (mean-centered) treatment response status (whether after treatment individuals had a MADRS reduction ≥ 50%) with 90% credible interval (shaded area). *Right:* The correlation between observed scores and the expected values for each individual. For (**A**) both treatment arms, (**B**) only those treated with CBT and fluoxetine, and (**C**) only those treated with CBT and a placebo.

reduced predictive accuracy observed in those treated with CBT and fluoxetine is generalizable to other SSRIs and/or antidepressant pharmacotherapies. Disentangling such factors in future work is necessary to determine precisely how these parameters may be clinically translatable.

Limitations

As the randomized controlled trial did not contain a treatment arm comprising placebo alone, it is difficult to disentangle which of the effects observed were prognostic effects and which are due to treatment with CBT. Our results were derived from young adults and adolescents and therefore requires replication in older depressed populations. Follow-up imaging data, which was not available, would have allowed us to determine whether the parameters that were different for treatment responders were normalized or exaggerated further through successful treatment. This is an important consideration for further research that may help to clarify why these parameters were predictive of response. While beyond the scope of our current model, both the posterior cingulate cortex and hippocampus have been shown to demonstrate depression associated alterations in activity. We selected not to include these regions as they have demonstrated limited evidence in predicting treatment response and in order to constrain the number of estimated model parameters.

CONCLUSIONS

While there have been a number of other studies examining effective connectivity in depressed adolescents [68, 85, 86], to our knowledge this is the first to examine how these parameters related to depression and treatment response during resting-state. As such, this research provides novel insight into how even in the absence of affective stimuli, there appears to be widespread alterations between intrinsic brain networks associated with the processing of these stimuli. Specifically, resting-state effective connectivity alterations associated with depression predominately involve inhibitory hyperconnectivity from the rACC. Similarly, our findings show that alterations between ACC regions, including the rACC and dACC, appear to predict response to treatment. This effect was shown to be particularly strong for those treated with CBT and a placebo. We proposed that this effect may be due to treatment with selective serotonin reuptake inhibitors resulting in these parameters being less useful predictors of response. These results highlight the potential utility of these parameters in treatment response prediction, however, future research will be necessary to disentangle the general prognostic effects and those specifically associated with CBT.

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AJJ: Conceptualization; Formal analysis; Methodology; Writing—original draft; Visualization. BJH: Conceptualization, Funding acquisition; Methodology, Supervision; Writing—review & editing. AR: Methodology, Writing—review & editing. CGD: Conceptualization, Funding acquisition; Methodology; Supervision; Writing—review & editing.

COMPETING INTERESTS

The authors declare no competing interests.

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