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Cognitive control circuit function predicts antidepressant outcomes: A signal detection approach to actionable clinical decisions

Leanne M. Williams [a,b,1,*], Jerome Yesavage [a,b,1]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA
[b] Mental Illness Research, Education and Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA 94304 USA

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ABSTRACT

Background: We previously identified a cognitive biotype of depression characterized by dysfunction of the brain's cognitive control circuit, comprising the dorsolateral prefrontal cortex (dLPFC) and dorsal anterior cingulate cortex (dACC), derived from functional magnetic resonance imaging (fMRI). We evaluate these circuit metrics as personalized predictors of antidepressant remission.

Methods: We undertook a secondary analysis of data from the international Study to Predict Optimized Treatment in Depression (iSPOT-D) for 159 patients who completed fMRI during a GoNoGo task, 8 weeks treatment with one of three study antidepressants and who were assessed for remission status (Hamilton Depression Rating Scale score of ≤ 7). Circuit predictors of remission were dLPFC and dACC activity and connectivity quantified in standard deviations. Using established software implementing receiver operating analysis (ROC) we calculated the sensitivity and specificity of these predictors at every cut-point for every circuit measure. We calculated number needed to treat (NNT) metrics for the ROC model identifying optimal cut-point values.

Results: ROC models identified maximum separation of remitters (62.5%) from non-remitters (21.2%) at an initial cut-point of −0.75 standard deviations for dLPFC activity and averaged circuit metrics at secondary cutpoints. The NNT was 3.72, implying that if 4 patients (rounding of 3.72) were randomly selected, one would be likely to remit, but if circuit metrics informed treatment, two would be likely to remit.

Conclusions: Our findings contribute to identifying clinically actionable circuit measures for clinical trials and clinical practice. Future studies are needed to replicate these findings and expand the assessment of longer-term outcomes.

Introduction

Major depressive disorder (MDD) remains a public health crisis in the U.S. and worldwide [1,2]. MDD is the most prevalent of mood disorders and the leading cause of disability worldwide [1,2]. From an economic standpoint, among all of medical conditions, major depression is associated with the largest direct and indirect costs for individuals and society, including a negative impact on time management and lost productivity [3,4]. Despite this lifetime burden due to MDD, we lack tools for selecting the most effective treatment for each patient. While antidepressant medications are effective on average, a third to one half of patients with MDD do not respond to these medications, even after multiple attempts [5]. New and emerging treatments are available to those for whom MDD does not respond to conventional antidepressants [6], such as repetitive transcranial magnetic stimulation (TMS), but we lack strategies for expediting access to these new treatment options.

Precision medicine applied in psychiatry seeks to address this need. The precision strategy is to use objective tests to identify the root cause of depression in each patient and to use this test information to aid in the selection of treatments. There is a growing evidence base showing that MDD comprises multiple different types of circuit dysfunction that may be conflated when we consider MDD as an umbrella diagnostic category [7–10]. Progress has been made in demonstrating that circuit dysfunction predicts antidepressant response and can differentiate response and non-response to different types of treatment [6]. To advance the clinically actionable utility of circuit measures derived from fMRI, there is a need for data on predictive models that evaluate whether the use of circuit predictors could improve the number of patients who achieve a

* Corresponding author.
E-mail address: leawilliams@stanford.edu (L.M. Williams).
[1] Co-authors contributed equally to this manuscript.

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therapeutic response. In this study, we used a prior established signal detection approach suited to clinically actionable decisions [11].

We focused on the cognitive control circuit implicated in cognitive impairment in MDD [12]. Cognitive impairment is recognized as a major contributor to both poor functional outcomes and lack of symptom relief from antidepressant treatments [13]. Using fMRI we have shown previously that dysfunction of the brain's cognitive control circuit, comprising the dorsolateral prefrontal cortex (dLPFC) and dorsal anterior cingulate cortex (dACC), derived from fMRI, characterizes a cognitive biotype of MDD [12]. The cognitive control circuit, defined by activity of the dLPFC and dACC, and functional connectivity between these regions, can be engaged by a Go-NoGo task and is implicated in response to SSRIs and SNRIs [14–16].

We have developed a precision medicine imaging technology to quantify circuit function in each individual patient relative to a healthy reference dataset [17]. This imaging system quantifies the cognitive control circuit in MDD and has demonstrated reliability, validity and generalizability, as well as sensitivity to individual variation [17]. In this study, we used cognitive control circuit measures as inputs to the novel signal detection technique in a secondary analysis of patients from the international Study to Predict Optimized Treatment in Depression (iSPOT-D). In iSPOT-D, patients were scanned with fMRI during a Go-NoGo task at the pre-treatment baseline, randomized to escitalopram, sertraline or venlafaxine-XR, and assessed for clinical remission outcomes after 8 weeks of treatment [18].

Methods

Subjects

Participants were patients from the international Study to Predict Optimized Treatment in Depression (iSPOT-D) who met criteria for first-onset or recurrent, nonpsychotic MDD according to DSM-IV criteria using a structured clinical Mini-International Neuropsychiatric Interview [19] and the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) [20] score of $\geq$ 16 [21]. Exclusion criteria included bipolar disorder, any psychosis, and/or neurocognitive disorder. Patients were free from pharmacotherapy, behavioral therapy, and other forms of therapy at baseline [22]. A total of 202 patients completed fMRI pre-treatment and, of these we focused on the 159 who also completed treatment and were assessed for remission outcomes.

Study drugs

After the baseline fMRI scan, patients were randomized to one of the three of the most widely used antidepressants, the SSRIs escitalopram and sertraline and the SNRI venlafaxine-XR.

Symptom assessments

At the pre-treatment baseline and following 8 weeks of treatment, patients were assessed clinically using the Quick Inventory of Depressive Symptoms (QIDS) [21]. Remission was defined as a post-treatment QIDS score of $\leq$ 5.

Neuroimaging (fMRI) technology

We have developed a precision medicine imaging technology to quantify circuit function in each individual patient relative to a healthy reference dataset [17]. This imaging system quantifies the cognitive control circuit in MDD and has demonstrated reliability, validity and generalizability, as well as sensitivity to individual variation [17].

Go-NoGo task

Functional magnetic resonance imaging was undertaken during an established Go-NoGo cognitive control task. This task reliably engages the cognitive control circuit of interest and activity in the dLPFC and dACC. Cognitive control was assessed using a Go-NoGo task. 'Go' trials (the word "press" in green), required subjects to respond as quickly as possible, while in the 'NoGo' trials ("press" in red) subjects were to withhold responses. 180 Go and 60 NoGo stimuli were presented in pseudorandom order: 500 ms each with an interstimulus interval of 750 ms. Head motion was restricted with foam pads and subject alertness was monitored with an eye-tracking system.

A high-resolution structural scan was also acquired for registration of functional images.

Image pre-processing

Author LMW has developed a standardized fMRI technology for implementing pre-processing and quantification of activation and functional connectivity at an individual subject level [17]. Motion correction is implemented with scripts that use well established procedures [23,24] to realign and unwarp the fMRI images to the first image of each task run. T1-weighted images are normalized to Montreal Neurological Institute (MNI) space using the FMRIB nonlinear registration tool, and fMRI data are coregistered to the T1 data using the FMRIB linear registration tool [25]. We also ensured that scans with incidental findings, major scanner artifacts, and signal dropout were not included.

Quantification of region of interest activation

Using the established imaging pipeline [17] with inputs from quality controlled fMRI data we then quantified blood-level-dependent activity in control circuit regions of interest for the contrast of NoGo versus Go stimuli. The defining regions for the cognitive control circuit are the dorsal lateral prefrontal cortex (dLPFC), left and right sided, and the dorsal anterior cingulate cortex (dACC). a standardized fMRI technology for implementing pre-processing and quantification of activation and functional connectivity at an individual subject level [17]. We have established masks for these regions of interest that meet quality control criteria including adequate gray matter overlap [17]. Task-evoked activity was quantified using a generalized linear model analysis in which task events were convolved with a canonical hemodynamic response. Activation in dLPFC and dACC were expressed in z-score standard deviation units relative to mean and standard deviation of a healthy reference dataset acquired on the same scanner. Task-related connectivity between dLPFC and dACC, in each direction, was quantified using a psychophysiological interaction (PPI) method for the NoGo versus Go contrast. This approach to quantifying clinical subject level data has been validated in our prior work [17].

In total seven metrics were generated for the cognitive control circuit: left dLPFC activation, right dLPFC activation, dACC activation, left dLPFC-dACC PPI, dACC-left dLPFC, right dLPFC-dACC PPI and dACC-dLPFC PPI.

Analyses

We used a novel application of a signal detection technique, receiver operator characteristics (ROC), to describe cognitive control circuit metrics that predict remission versus non-remission to the 159 patients with complete who had complete pre-treatment fMRI data and who completed treatment on one of the three study drugs.

ROC software

The software used in this analysis was developed at the Sierra-Pacific MIRECC and is in the public domain (https://web.stanford.edu/~yesavage/ROC.html). The ROC software tests for the optimal sensitivity and specificity for identifying those particular patients with the specific clinically relevant outcome of interest. In this study the outcome of interest in remission. The ROC tests every predictor variable (in this case, circuit variables) and every possible cut-point value for that variable for every subject in the database. Once the optimal predictor variable and

associated cut-point are identified, the association with the outcome of interest (in this case, remission) is tested with a stopping rule. If the association with remission passes the rule, the sample is divided into two subgroups according to the optimal predictor variable and optimal cut-point. The ROC analysis is then restarted, separately, for each of these two subgroups. The ROC procedure again examines every circuit predictor variable for every subject and cut-point to see if either subgroup can be further separated. The procedure will stop when it hits the stopping rule or when a subgroup has too small (less than 10) a sample size for further analysis[11]. The final result is a decision tree.

Data reduction

In the original work establishing the circuit quantification technology we established the internal consistency of the cognitive control circuit metrics[17]. We examined the intercorrelations of the seven cognitive control metrics for the present sample, reported in Table 1. Higher correlations are seen among variables that belong to the same putative domains, namely activation with activation and PPI with PPI metrics, than those correlations seen between domains, namely activation with PPI metrics (Table 1). Because each of the cognitive control circuit metrics represents a standardized score, we calculated summary standardized scores for the three activation metrics ('Activation average')_and for the four PPI metrics ('PPI average') from their arithmetic averages. We also calculated an average of all seven metrics ('Circuit average') to determine if it might be more robust than any of the separate cognitive control circuit metrics or their domain averages as a predictor of remission.

Results

In this exploratory analysis, four different sets of ROC analyses were performed, each using a different data reduction method for the cognitive control circuit predictor data to test the association with remission. These included all possible combinations of the individual circuit metrics, as well as Activation and PPI averages and a Circuit average score:

1. A Circuit grand average score which was the overall average of all seven cognitive control circuit metrics.
2. Activation and PPI average scores calculated as the arithmetic mean of the standardized metrics for the three activation scores and the four PPI metrics respectively.
3. The individual standardized circuits scores of all seven circuit metrics.
4. A "Hybrid" model that included both average scores (Activation, PPI) and the seven individual circuit metrics.

Figs. 1–4 represent the four decision trees based upon the four ROC analyses. Each tree starts with the total of 159 cases in which the base remission rate is 35.8 %, a rounded proportion of 0.36. In each analysis, the next box reports the first-cut point selected by the ROC that represents the threshold at which there is the best sensitivity and specificity for identifying remitters. The 159 is divided into those who meet the cut-point threshold or not. The boxes on the right side of the ROC figure report the percentage of patients who were actually remitters based on this cut-point. In Fig. 1, this percentage is 41.1 %. This percentage is further reflected in the Positive Predictive Value (PPV) of 0.411, determined by the number of accurately identified remitters divided by this number of remitters plus false positives. In the second model in Fig. 2, the cut-point by PPI average plus the Activation average separated a higher percentage of accurately identified remitters (55.1 %) with a PPV of 0.551. For the third model evaluating individual circuit scores, the best selected variable, right dLPFC activation, plus the next step down split on a second variable, dACC activation, resulted in a separation of 56.4 % correctly identified remitters with a PPV of 0.564 (Fig. 3). The Hybrid model produced the maximum separation of remitters with the first cut-point splitting by right dLPFC activation at the first cut-point, and the next step down cut-point splitting on the second variable, average PPI, correctly identifying 62.5 % with a PPV of 0.625.

Table 2 presents the results of these four ROC analyses, highlighting the circuit measures selected, their cut-points and the sensitivity and specificity of those cut-points to predict remission as measured by the HRSD.

Number needed to treat

To further assess the clinical meaningfulness of the ROC results, we calculated number needed to treat (NNT) metrics. NNT was calculated using the following formula:

NNT = 1/ARR.

ARR = Control event rate – Experimental event rate.

Our control event rate (population remission rate) is 35.8 %, rounded up to and expressed as a proportion, 0.36. The experimental event rate is the percentage of correctly identified remitters for each ROC model, rounded to a whole proportion with two decimal places.

NNT results presented for each model, ordered from highest NNT to the lowest (best) NNT as follows:

1. Circuit average model

   Experimental event rate = 0.41.
   Thus, ARR = 0.36–0.41 = 0.05.
   Thus, NNT = 1/0.05 = 20.

2. Activation and PPI averages, with circuit average

Table 1
Correlation matrix of cognitive control circuit metrics derived from fMRI.

		Activation metrics			PPI metrics		
		Right_dLPFC activation	dACC activation	Left dLPFC-dACC PPI_	dACC-Left dlPFC PPI	Right dLPFC-_dACC PPI	dACC-Right_dLPFC PPI
Activation metrics	Left dlPFC activation	**0.46**	**0.57**	−0.14	−0.03	−0.06	0.05
	Right dlPFC activation		**0.49**	0.06	0.09	−0.01	0.03
	dACC activation			−0.03	0.13	−0.05	0.08
PPI metrics	Left dlPFC-dACC PPI				**0.49**	**0.61**	**0.38**
	dACC-Left dLPFC PPI					**0.32**	**0.42**
	Right dlPFC- dACC PPI						**0.45**

Legend: Higher correlations are seen among variables that belong to the same putative domains (Activation with Activation metrics, light red shading, and PPI with PPI metrics, paler red shading), than those correlations seen between domains (Activation with PPI metrics, gray shading). Bold font indicates significant at $p < .001$.

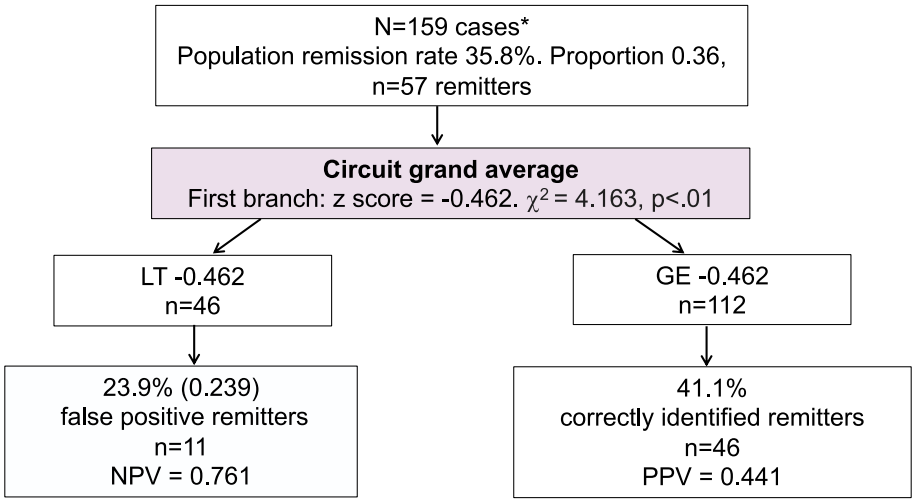

Fig. 1. ROC for remission predicted by the Circuit grand average. Maximum separation of correctly identified remitters was 41.1% remission versus the base rate of 35.8%. Sensitivity was 0.807, specificity was 0.347 and kappa was 0.132. *One data point was excluded as missing.

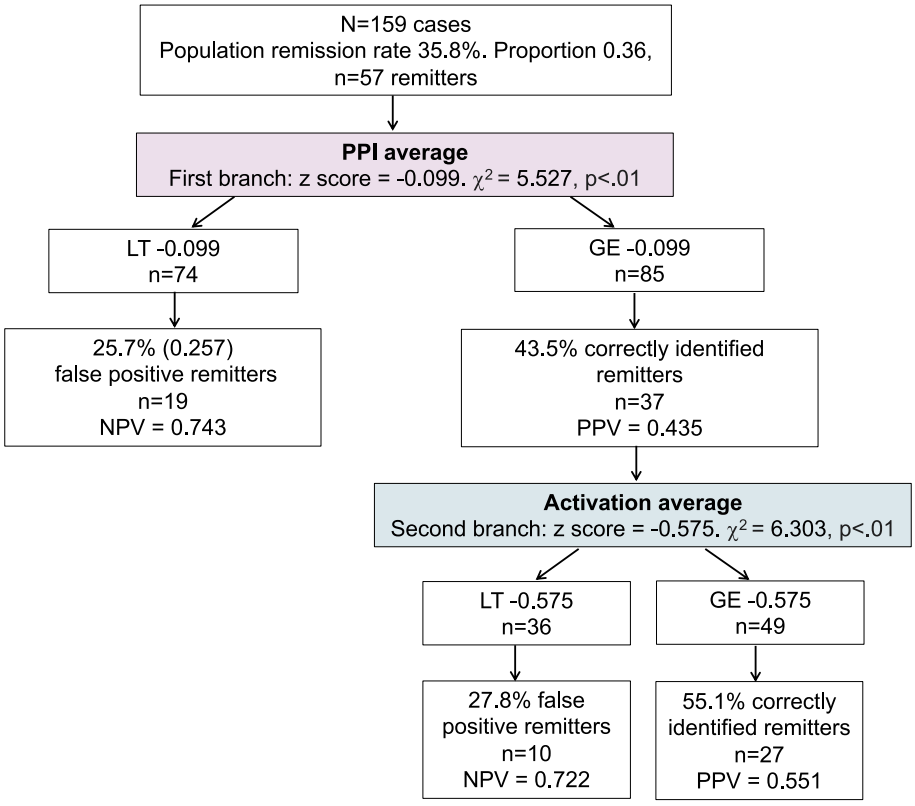

Fig. 2. ROC for remission predicted by the Activation average and PPI average with the Circuit average. Activation and PPI average scores predicted remission better than the Circuit grand average score. Maximum separation of correctly identified remitters was 55.1% versus the base rate of 35.8%. Sensitivity was 0.734, specificity was 0.544 and kappa was 0.262.

Experimental event rate = 0.55.
Thus, ARR = 0.36–0.55 = 0.19.
Thus, NNT = 1/0.19 = 5.26.

3. Individual Activation and PPI metrics

Experimental event rate = 0.56.
Thus, ARR = 0.36–0.56 = 0.20.
Thus, NNT = 1/0.20 = 5.

4. Hybrid model

Experimental event rate = 0.63 %.
Thus, ARR = 0.36–0.63 = 0.27.
Thus, NNT = 1/0.27 = 3.70.

Let us apply the interpretation of NNT to these results, focusing on the hybrid model:

1. As is the custom, we conservatively round up the 3.70 NNT to 4.

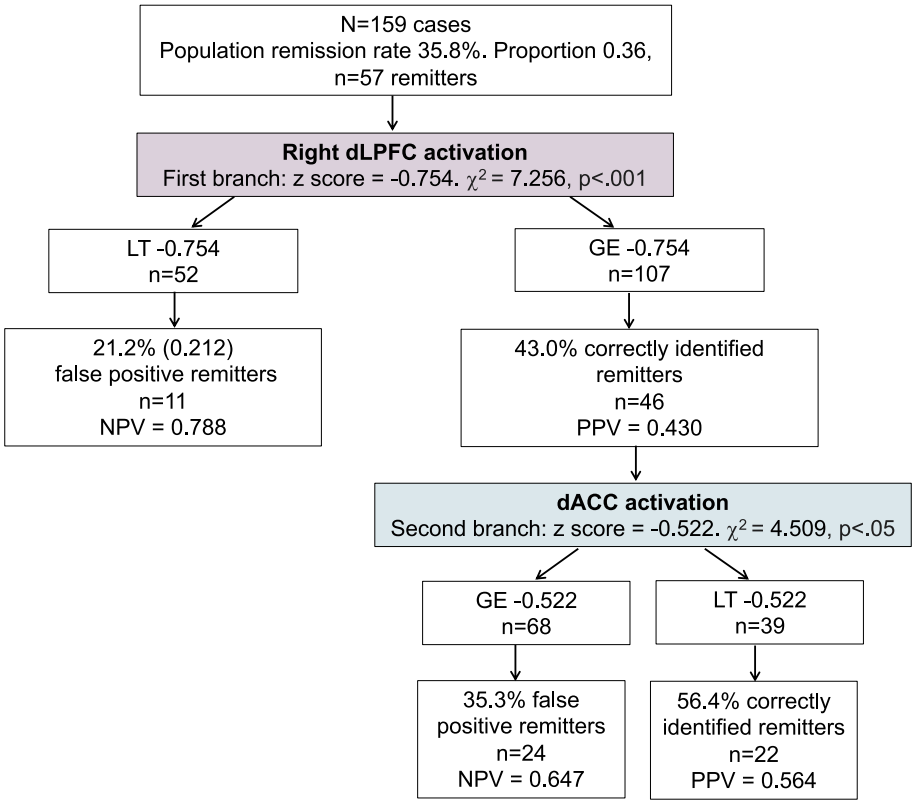

Fig. 3. ROC for remission predicted by the seven individual circuit metrics. Maximum separation of correctly identified remitters was 56.4% versus the base rate of 35.8%. Sensitivity was 0.833, specificity was 0.477 and kappa was 0.203.

2. The base population remission rate is 36 %; with the optimized fMRI selection procedure, we can prospectively identify a higher rate of individuals who will achieve remission, raising the rate to 63 %.
3. Then, using an NNT of 4, one could expect 1.44 remissions in the unselected patients (36 % of 4), but 2.52 with the improvement in identification of remitters (63 % of 4).
4. The difference between 2.52 and 1.44 represents one less patient with a failed treatment.

Discussion

In a secondary analysis of data from 159 patients from the iSPOT-D trial, we derived cognitive control circuit metrics using an image processing method designed to quantify fMRI data at the individual patient level. These circuit measures were inputs into an established software, implementing ROC to calculate the sensitivity, specificity and predictive power of circuit predictors of antidepressant remission outcomes at every possible cut-point value for every predictor. The best results in terms of the maximum separation of remitters correctly identified 63 % of remitters versus the base rate of 36 %. Circuit predictors in this model, the 'hybrid' model, combined an initial cut-point of −0.75 standard deviations for dLPFC activity with an average of connectivity and activation scores at secondary cut-points.

Within the hybrid model the right dLPFC was the primary contributor to correct prediction of remission status. In our prior work the right dLPFC also shows relatively greater impairment than the left dLPFC in characterizing the cognitive control biotype of depression [12]. The right dlPFC has been specifically implicated in the online adjustment of cognitive control, including the flexible adaption to dynamic task demands [26,27]. These findings regarding lateralized dLPFC functions suggest that the right dLPFC not only contributes to the mechanisms of the cognitive control biotype but also to identifying likelihood of remitting on commonly prescribed antidepressants.

We emphasize that the ROC strategy used in this analysis is a data exploration technique and that results in a sample of this size must be replicated. Nonetheless, there are some suggestions for further study, including in prospective trial designs that assess longitudinal outcomes over a longer time frame than in the present dataset. Ultimately the best set of circuit predictors will be resolved with a combination of empirical data, a trial in the field where the sought-after signal and the surrounding noise will vary with each setting and clinician consensus.

Implications for precision medicine in psychiatry

Our findings contribute to the broader goal of precision medicine in psychiatry to develop clinically actionable measures that could be used in routine clinical practice. A number of national initiatives have been launched to make progress toward this goal, including the National Institute of Mental Health Research Domain Criteria initiative [28,29]; and the NIH BRAIN Initiative [30]. More recently, Congress passed the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019, which instructs the Veterans Administration to implement the Precision Mental Health for Veterans Initiative to identify and validate brain and mental health biomarkers among veterans, with specific consideration for depression, anxiety, PTSD, bipolar disorder, and traumatic brain injury [31]. Under this initiative, the methods should include brain structure and function measurements, such as functional magnetic resonance imaging, aligned with the focus of our study and findings.

Clinical and economic implications of optimizing remission outcomes

We have described the NNT as the number of patients needed to treat with a new treatment to prevent one additional bad outcome: death, stroke, or—in our case—failure to remit after antidepressant therapy. For example, if an antidepressant has an NNT of 5, it means you must

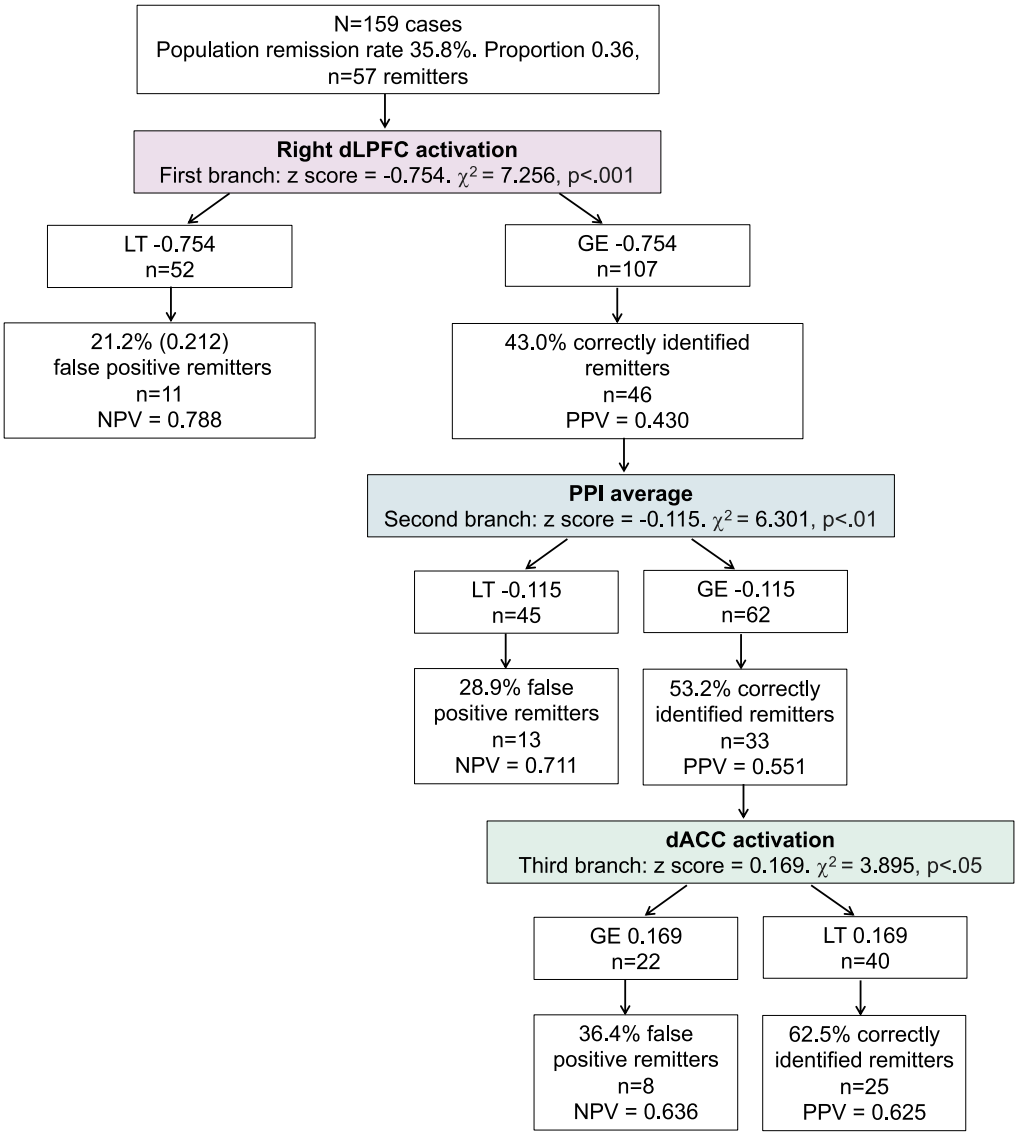

Fig. 4. ROC for remission predicted by the Hybrid model, combining the Activation and PPI averages with the seven individual circuit metrics. Within the hybrid model the best overall predictor of remission, included in the decision tree with average scores and all seven individual metrics, was right dlPFC activation. Maximum separation of correctly identified remitters was 62.5% remission versus the base rate of 35.8%. Sensitivity was 0.758, specificity was 0.483 and kappa was 0.244. This was the best performing of the models.

Table 2
Summary of Best Prediction of Remission in Four ROC Models.

Best Variable		Cut-Point	Sens	Spec	kappa	chi square, χ^2	% correctly identified remitters	NNT
Circuit Average Score (Fig. 1)								
Branch 1. Circuit average	GE	−0.462	0.80	0.35	0.132	4.493	41.1 %	18.28
Activation average and PPI average with Circuit Average (Fig. 2)								
Branch 1. PPI average	GE	−0.099	0.66	0.53	0.174	5.527		
Branch 2. Activation average	GE	−0.575	0.730	0.542	0.262	6.303	55.1 %	5.14
Individual Activation and PPI scores (Fig. 3)								
Branch 1. Right dlPFC activation	GE	−0.754	0.807	0.402	0.175	7.256		
Branch 2. dACC activation	LT	−0.522	0.478	0.721	0.203	4.509	56.4 %	4.81
Hybrid (Fig. 4)								
Branch 1. Right dLPFC activation	GE	−0.754	0.807	0.402	0.175	7.256		
Branch 2. PPI average	GE	−0.115	0.717	0.525	0.232	6.301		
Branch 3. dACC activation	LT	0.169	0.758	0.483	0.244	3.895	62.5 %.	3.72

Note: Color code shading refers to first, second and third decision tree branches. Corresponding color codes are also used in Figs. 1-4 in the Decision Tree Diagrams. NNT = Number needed to treat.

treat 5 people with the drug to prevent one additional failure to remit compared to a standard treatment. Our optimized hybrid fMRI selection model has an NNT of 4. Thus, for every 4 patients using the optimized fMRI model to select treatment prevents one additional failure to remit compared to unselected patients. The remission rate increases from the entire population rate of 36 % for unselected patients to 63 % using the optimized fMRI model.

Creating a larger economic example may show the importance of NNT calculations. Take treating 100 typical patients, you would expect 36 remissions in an unselected population (36 % of 100). Using fMRI selection, were it to work in the field, one would only have to treat 58 patients meeting the selection criteria to obtain the same number of remissions (62 % of 58). Thus, if the treatment cost is $10,000 per course, the fMRI of selected patients would only cost $580,000 to treat (58 times $10,000) versus $1,000,000 (100 times $10,000) for the same number of successes in an unselected population. Such an approach at a health systems level might afford considerable savings, even if one had to spend $58,000 to get 58 fMRIs at $1000 each. Finally, it might also afford a considerable reduction in frustration of patients and physicians alike by avoiding a treatment that has a near 2/3 risk of being doomed to failure.

Finally, boosting the number of patients achieving remission based on pre-treatment circuit predictors has the further potential to help drive down the longer-term costs due to burden of illness in depression. Reflecting some aspects of the burden of illness, for every employee experiencing depression, there is an average cost of $15,000 per year in lost productivity, health care costs and turnover[32]. Based on this annual cost, using the current clinical heuristic, one individual achieving remission out of three would reduce lost productivity costs from $45,000 to $30,000. In the future, if the incorporation of circuit predictors enables two out of three individuals to achieve remission, this cost could be reduced further, from $45,000 to $15,000. Depression has a chronic course of disability, resulting in lifetime costs that are currently not routinely factored in when evaluating the introduction of new clinical tools, such as neuroimaging, in psychiatry.

In conclusion, our findings contribute to the broader goal of precision medicine in psychiatry to develop biomarkers that align with national initiatives and that could be used in clinical trials in the field and in clinical practice. Future studies are needed to replicate these findings and to consider expanding them to a longer-term assessment of outcome.

CRediT authorship contribution statement

Leanne M. Williams: Writing – original draft, Software, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Jerome Yesavage:** Writing – original draft, Software, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: LMW declares US Pants. App. 10/034,645 and 15/820,338: Systems and methods for detecting complex networks in MRI image data. Yesavage declares no competing interests.

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