

# Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder

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**Background:** Longitudinal neuroimaging investigations of antidepressant treatment offer the opportunity to identify potential baseline biomarkers associated with poor outcome. **Methods:** To explore the neural correlates of nonresponse to cognitive behavioural therapy (CBT) or venlafaxine (VEN), we compared pretreatment (18)F-fluoro-2-deoxy-D-glucose positron emission tomography scans of participants with major depressive disorder responding to either 16 weeks of CBT ( $n = 7$ ) or VEN treatment ( $n = 9$ ) with treatment nonresponders ( $n = 8$ ). **Results:** Nonresponders to CBT or VEN, in contrast to responders, exhibited pretreatment hypermetabolism at the interface of the pregenual and subgenual cingulate cortices. **Limitations:** Limitations of our study include the small sample sizes and the absence of both arterial sampling to determine absolute glucose metabolism and high-resolution structural magnetic resonance imaging coregistration for region-of-interest analyses. **Conclusion:** Our current findings are consistent with those reported in previous studies of relative hyperactivity in the ventral anterior cingulate cortex in treatment-resistant populations.

**Contexte :** Les études de neuro-imagerie longitudinales pendant le traitement antidépresseur offrent la possibilité de repérer certains biomarqueurs de base susceptibles d'être associés à une évolution moins favorable. **Méthodes :** Pour explorer les corrélats neuraux propres au phénomène de résistance à la thérapie cognitivo-comportementale (TCC) ou au traitement par venlafaxine (VEN), nous avons comparé les tomographies par émission de positrons au (18)F-fluoro-2-désoxy-D-glucose préthérapeutiques de participants atteints de troubles dépressifs majeurs qui ont répondu soit à 16 semaines de TCC ( $n = 7$ ), soit à un traitement par VEN ( $n = 9$ ), à celles de participants n'ayant pas répondu au traitement ( $n = 8$ ). **Résultats :** Comparativement aux participants ayant répondu au traitement, ceux qui n'ont répondu ni à la TCC ni à la VEN présentaient en prétraitement un hypermétabolisme au niveau de l'interface du cortex cingulaire ventro-antérieur du genou du corps calleux. **Limites :** Les limites de notre étude sont notamment la petite taille des échantillons et l'absence à la fois de prélèvements artériels pour déterminer le métabolisme absolu du glucose et d'enregistrements simultanés d'imagerie par résonance magnétique structurale de haute résolution à des fins d'analyse des régions concernées. **Conclusion :** Nos résultats actuels concordent avec ceux d'études antérieures sur l'hyperactivité relative du cortex cingulaire ventro-antérieur dans le traitement des populations réfractaires au traitement.

## Introduction

The 2 most established acute treatment modalities for major depressive disorder (MDD) are pharmacotherapy and evidence-based psychotherapy, particularly cognitive behavioural therapy (CBT). Both have roughly comparable out-

comes.<sup>1,2</sup> Nevertheless, up to 50% of patients fail to achieve an adequate response, and even fewer achieve remission following an acute treatment trial.<sup>3</sup> Despite advances in neurosciences, cognitive sciences and psychopharmacology, there is no current algorithm to guide optimal treatment selection for individual patients.<sup>4,5</sup>

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Response prediction based on clinical parameters, including symptom clusters or depressive subtype, has yielded disappointing results.<sup>6</sup> Early neurobiological predictors, including neuroendocrine markers<sup>7,8</sup> and electrophysiological recordings,<sup>9,10</sup> have not had a substantial impact on treatment selection, although 2 rapidly advancing techniques that may offer superior predictive value are pharmacogenetics<sup>11,12</sup> and functional neuroimaging.<sup>13,14</sup>

Neuroimaging investigations employing (18)F-fluoro-2-deoxy-D-glucose positron emission tomography and electroencephalography suggest that baseline metabolism in the pregenual cingulate (Brodmann area [BA] 24) and subgenual cingulate (BA 24/25) cortices may predict response to various antidepressant interventions including pharmacotherapy,<sup>15–19</sup> sleep deprivation<sup>20</sup> and cingulotomy.<sup>21</sup> In 2 of 4 pharmacotherapy investigations, lower pretreatment metabolic activity in the anterior cingulate cortex (ACC) predicted favourable response, whereas higher activity in the pregenual ACC predicted response in the other 2.<sup>17,18</sup> To date, there have been fewer investigations of metabolic changes following psychological interventions,<sup>22–25</sup> and these have not distinguished between treatment responders and nonresponders.

We have previously reported on the differential effects of venlafaxine (VEN) and CBT in altering brain glucose metabolism following a 16-week randomized controlled trial to treat MDD.<sup>26</sup> However, there was no assessment of baseline scans as potential predictors of response or nonresponse. The purpose of the present analysis is to examine baseline metabolism in the same population as a predictor of antidepressant nonresponse to CBT and VEN in this clinical population. We hypothesized that baseline metabolism in either the pregenual or subgenual cingulate cortices would have predictive value.

## Methods

We recruited patients aged 20–50 years at the Centre for Addiction and Mental Health at the University of Toronto, Toronto, Ont. Participants were required to meet the DSM-IV criteria for MDD in the context of a current major depressive episode, as assessed by the Structured Clinical Interview for DSM-IV, patient version (SCID-IP),<sup>27</sup> and score 20 or greater on the Hamilton Rating Scale for Depression, 17-item version (HAM-D-17).<sup>28</sup> Antidepressant medication-free status for at least 2 weeks (4 weeks for fluoxetine) preceding the study and good physical health with no evidence of neurologic or other unstable medical conditions were additional inclusion criteria. Other Axis I diagnoses, including concurrent anxiety disorders and substance abuse or dependence within the 6 months preceding the study, evidence of active suicidal ideation, pregnancy and previous failure to respond to an adequate trial of CBT or VEN were exclusion criteria. All participants provided written informed consent. The Research Ethics Board of the Centre for Addiction and Mental Health approved our study.

We randomly assigned participants to receive either VEN (75–225 mg/d) or CBT for 16 weeks. We assessed the severity of depressive symptoms using the HAM-D-17. We defined

response to treatment as a minimum reduction of 50% in HAM-D-17 scores from baseline to end point.<sup>29</sup>

We obtained positron emission tomography measurements of regional cerebral glucose metabolism within 1 week before treatment initiation and within 1 week of the last treatment visit. For each scan, we injected a 5-mCi (185-Mbq) dose of (18)F-fluoro-2-deoxy-D-glucose intravenously, with image acquisition beginning after 40 minutes (PC 2048b; GEMS-Scanditronix). We acquired all scans at a consistent time, between 9 am and noon, with participants in a supine, awake and resting state with eyes closed and ears uncovered. We asked participants to refrain from food, coffee or alcohol intake for a minimum of 8 hours before each scan session.

We gave participants no explicit cognitive instructions, but we asked them to avoid ruminating on any one topic during the (18)F-fluoro-2-deoxy-D-glucose uptake period. A member of the research staff monitored wakefulness every 10 minutes. We acquired emission data during a 35-minute period (about 1 million counts per slice; 10-cm field of view). We used a customized, thermoplastic face mask to minimize head movement. We corrected raw images (15 parallel slices; 6.5-mm centre-to-centre interslice distance) for attenuation, and we reconstructed and smoothed them to a final in-plane resolution of 7.0 mm at full width at half maximum.

## Statistical analysis

We performed all statistical analyses using SPM99 statistical software (Wellcome Department of Cognitive Neurology, London, England) and Matlab (version 7.4; Mathworks Inc.). We normalized all scans to the Montreal Neurological Institute ICBM 152 stereotactic template within SPM99. We normalized the scans for differences in whole-brain global metabolism by setting the mean voxel value of each image to 1.0, and we smoothed them, using a Gaussian kernel, to a final in-plane resolution of 12 mm at full width at half maximum. We did not calculate absolute glucose metabolic rates.

For the regions of the pregenual and subgenual cingulate cortices defined a priori, we evaluated clusters meeting the “minimum expected cluster size in SPM” ( $k > 74$ ) and the uncorrected  $p < 0.01$  height threshold for differences in relative regional glucose metabolism between nonresponder and responder groups. We also evaluated supplementary between-group comparisons across the whole brain (CBT nonresponders v. responders and VEN nonresponders v. responders) at an uncorrected  $p < 0.001$  height threshold. We converted the resulting  $F$  values to  $z$  scores, with brain locations reported as  $x$ ,  $y$ , and  $z$  coordinates in Montreal Neurological Institute space with approximate BA identified by mathematical transformation of SPM99 coordinates into Talairach space.<sup>26</sup>

## Results

Thirty-one patients (13 men and 18 women) participated in our study. Of these, we randomly assigned 14 to the VEN group and 17 to the CBT group. After random assignment, 4 patients failed to return to initiate treatment (CBT,  $n = 3$ ;

VEN,  $n = 1$ ). During the 16-week treatment phase, 1 patient discontinued VEN and 2 discontinued CBT owing to lack of efficacy. Characteristics of the remaining 12 patients in each group are provided in Table 1.

Nine participants treated with VEN and 7 treated with CBT responded to treatment. At baseline, there were no sta-

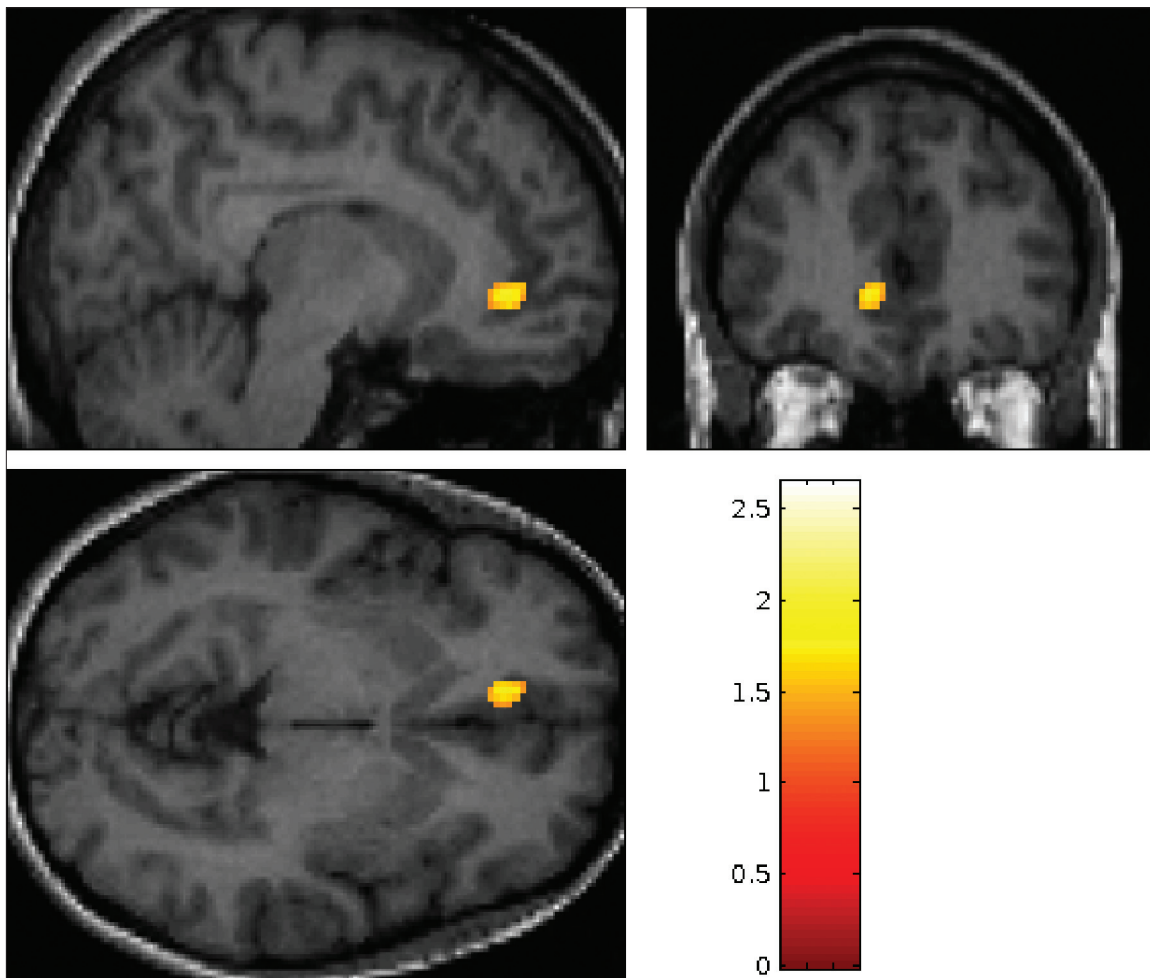
tistically significant differences in age or HAMD-17 scores between eventual responders and nonresponders (Table 1).

Nonresponders to either treatment modality displayed hypermetabolism at the interface between the pregenual and subgenual cingulate cortices (ventral ACC, BA 24/32), in contrast to responders (Fig. 1, Fig. 2, Table 2) ( $p < 0.012$ ). We

**Table 1: Characteristics of responders and nonresponders to treatment with venlafaxine or cognitive behavioural therapy for major depressive disorder**

Characteristic	Treatment group			
	Venlafaxine		Cognitive behavioural therapy	
	Responders	Nonresponders	Responders	Nonresponders
No. of patients	9	3	7	5
Age, mean (SD) yr	40.1 (8.6)	37.8 (12.0)	32.7 (11.4)	26.2 (6.1)
Female sex, %	44.4	100.0	71.4	40.0
HAMD-17 score, mean (SD)				
Baseline	20.0 (3.2)	21.0 (2.9)	19.6 (3.5)	22.0 (3.2)
End point	4.1 (1.1)	13.8 (1.3)	5.4 (3.8)	18.4 (3.9)

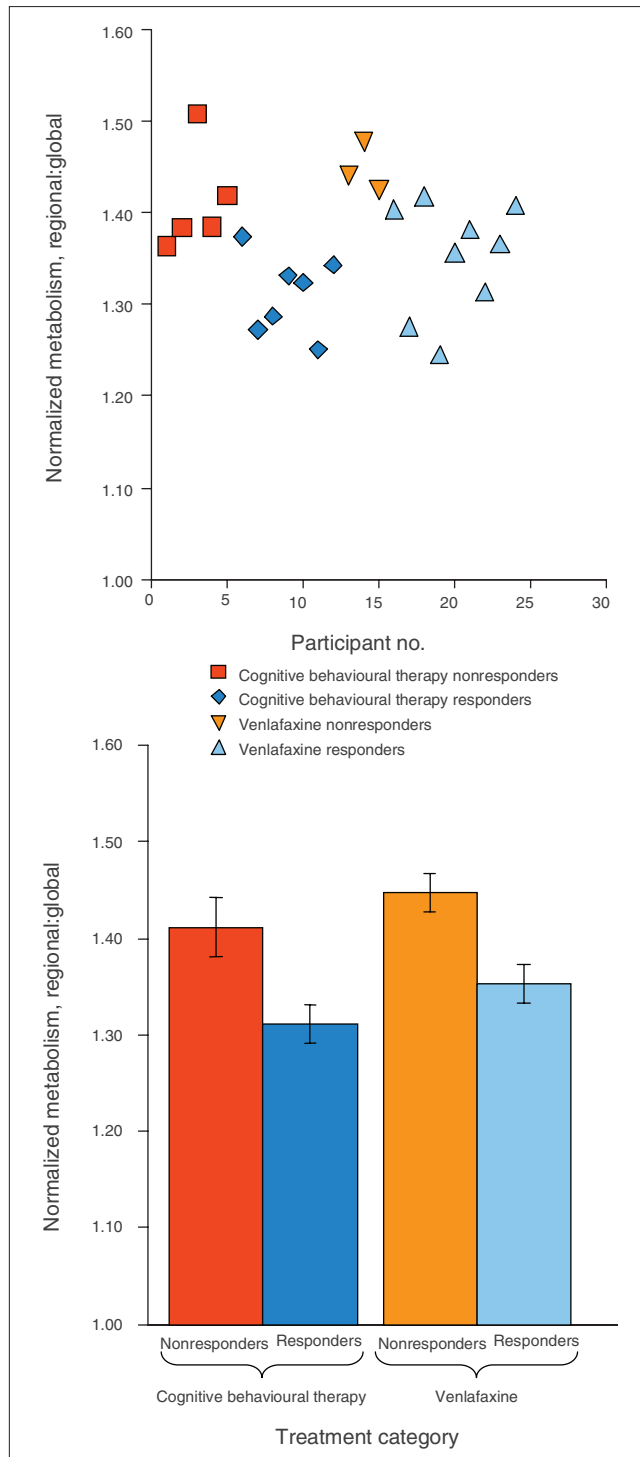
HAMD-17 = Hamilton Rating Scale for Depression, 17-item version<sup>28</sup>; SD = standard deviation.



**Fig. 1.** Ventral anterior cingulate cortex (Montreal Neurological Institute coordinates  $-10, 40, -04$ ) hypermetabolism in nonresponders to either treatment (pooled nonresponders,  $n = 8 >$  pooled responders,  $n = 16$ ,  $p < 0.01$  uncorrected,  $k > 74$ ).

noted no other statistically significant differences in glucose metabolism between the group of pooled responders ( $n = 16$ ) and nonresponders ( $n = 8$ ).

Subsequent analyses focused on responder/nonresponder differences within each treatment arm. Unique to the



**Fig. 2.** Hypermetabolism in nonresponders to either treatment ( $p > 0.01$  uncorrected,  $k > 74$ ).

CBT groups, nonresponders (in contrast to responders) also displayed hypermetabolism in the parahippocampal gyrus (BA 36/37) ( $p < 0.001$ ) and dorsal occipital cortex (BA 19) ( $p < 0.001$ ) (Table 2). In the VEN group, decreased baseline metabolism in the cerebellum differentiated eventual nonresponders from responders ( $p < 0.001$ ) (Table 2). It should be noted that owing to the small sample size involved, these reported differences must be considered very preliminary, and will not be discussed further, but are included for completeness.

## Discussion

Depressed participants who did not respond to treatment displayed relative hyperactivity in a region at the interface between the pregenual and subgenual cingulate cortices, in contrast to responders.

Pre-post investigations of changes in brain glucose metabolism during antidepressant response to disparate treatment modalities have consistently noted decreases in metabolism in the subgenual cingulate cortex.<sup>22,26,30-35</sup> Differences in baseline metabolism within subdivisions of the anterior cingulate gyrus have also been reported as predictors of nonresponse to treatment with selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. Hyperactivity in the subgenual portions of the ACC was associated with treatment nonresponse,<sup>16,36</sup> as was hypoactivity of the pregenual (rostral) ACC.<sup>17,18,37</sup>

Historically, the primary function ascribed to the ACC is affective processing.<sup>38</sup> Investigations of cytoarchitecture, connectivity and function of the ACC have divided the region that encompasses BAs 24, 25, 32 and 33 into 2 subdivisions with distinct functions: a dorsal cognitive division and a rostral-ventral affective division.<sup>39-41</sup> Mayberg<sup>42</sup> has hypothesized that the pregenual ACC represents an interface between these 2 subdivisions.

Using functional magnetic resonance imaging, hyperactivation of the subgenual cingulate cortex in response to emotional stimuli in participants with MDD ( $n = 14$ ) was associated with poor response to 16 sessions of CBT.<sup>43</sup> These findings raise the possibility that hyperactivity in the subgenual cingulate cortex predicts treatment resistance to both pharmacotherapy and psychotherapy. Indeed, in an evaluation of participants with MDD who had failed to respond to a minimum of 4 different antidepressant treatments, elevated blood flow in the subgenual cingulate cortex was noted in contrast to a healthy control group.<sup>34</sup> Hyperactivity in the ventral ACC has also been associated with other medication-resistant depressed populations seeking alternative antidepressant treatments.<sup>20,21</sup>

Mood and anxiety disorders are associated with dysfunctional limbic-cortical interactions, with illness remission being conceptualized as appropriate network modulation by various forms of treatment.<sup>33</sup> Furthermore, it has been proposed that an initial modulation of subcortical targets may be a necessary first step that facilitates subsequent adaptive changes in network homeostasis.<sup>14</sup> In support of this model, an evaluation of more than 100 depressed patients revealed



Table 2: Between-group differences in normalized glucose metabolism

Group; brain region	L/R	BA	Direction of change	Coordinates			Voxels in cluster	z score*
				x	y	z		
All nonresponders v. responders								
Ventral anterior cingulate cortex	L	24/32	↑	-10	40	-4	79	3.04
CBT nonresponders v. responders								
Dorsal occipital cortex	R	19	↑	36	-88	22	115	3.82
Parahippocampal gyrus	R	36/37	↑	20	-42	-14	67	3.54
VEN nonresponders v. responders								
Cerebellum	L	—	↓	-28	-82	-32	60	3.58

BA = Brodmann area; CBT = cognitive behavioural therapy; L = left; R = right; VEN = venlafaxine.

\*Scores above 2.34 correspond to  $p < 0.01$  uncorrected; scores above 3.12 correspond to  $p < 0.001$  uncorrected.

differences in connectivity between the dorsolateral prefrontal (BA 9), subgenual cingulate (BA 25) and orbitofrontal (BA 11) cortices between pharmacotherapy responders and nonresponders. Similarly, limbic-cortical connectivity also differentiated CBT responders from pharmacotherapy responders.<sup>44</sup> Our results are consistent with previous glucose investigations evaluating response to antidepressant treatment in patients with MDD in that nonresponders in our study demonstrated abnormalities in limbic-subcortical pathways involving parts of the pregenual (BA 24) and subgenual (BA 25) cortices and the ACC.<sup>13,15-17,20,43,45</sup>

### Limitations

Limitations of our study include the small sample sizes, particularly in the within-treatment comparisons, which limited our ability to detect low-magnitude differences. As such, our within-treatment comparison findings must be regarded as preliminary. Other limitations include the absence of both arterial sampling to determine absolute glucose metabolism and high-resolution structural magnetic resonance imaging coregistration for region-of-interest analyses. Additionally, it is worth noting that the methods employed in our analysis were more likely to identify baseline group differences after treatment than individual differences that could guide treatment selection.

Emergent evidence from cerebral blood flow, glucose metabolism and blood oxygenation studies indicates that alteration in subgenual cingulate cortex activity alone, or in concert with other limbic or cortical targets, may mediate severity of depressive symptoms and resistance to treatment.<sup>14,44</sup> Our report of hyperactivity in the pregenual and subgenual cortices of the ACC as a marker of nonresponse to both pharmacotherapy and psychotherapy further corroborates these results and complements extant models that emphasize comparable and distinct neural connectivity mediating the therapeutic effects of CBT and medication.<sup>44,45</sup>

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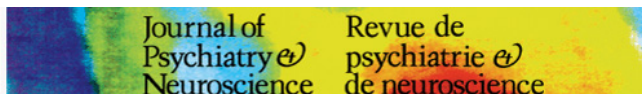
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**Contributors:** Drs. Mayberg, Kennedy and Segal designed the study. Mr. Konarski and Drs. Segal, Lau, Bieling and Mayberg acquired the data. Mr. Konarski and Drs. Kennedy and Mayberg analyzed the data. Mr. Konarski and Drs. Kennedy and McIntyre wrote the paper. Mr. Konarski and Drs. Kennedy, Segal, Lau, Bieling, McIntyre and Mayberg reviewed the article. All authors approved final publication.

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