Depressive Disorders: Focally Altered Cerebral Perfusion Measured with Arterial Spin-labeling MR Imaging[1]

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Purpose: To assess focal cerebral perfusion in patients with refractory depressive disorder (RDD), patients with nonrefractory depressive disorder (NDD), and healthy control subjects by using arterial spin-labeling (ASL) magnetic resonance (MR) imaging.

Materials and Methods: This study was approved by the local ethical committee, and written informed consent was obtained from all participants. Twenty-four patients with RDD, 37 patients with NDD, and 42 healthy control subjects were included. From February 2006 to July 2007, all participants were imaged with a 3-T MR system. ASL and echo-planar images were subtracted and averaged to give perfusion-weighted images. Voxel-based analysis was performed. Region-of-interest analysis was applied to the bilateral hippocampi, thalami, and lentiform nuclei.

Results: Patients with NDD showed reduced perfusion in the left prefrontal cortex versus control subjects and increased perfusion mainly in the limbic-striatal areas ($P < .05$). In contrast, patients with RDD had decreased perfusion predominantly in the bilateral frontal and bilateral thalamic regions ($P < .05$). Compared with patients with RDD, patients with NDD showed higher perfusion mainly in the limbic-striatal areas ($P < .05$). In region-of-interest analysis, the NDD group showed higher regional cerebral blood flow than both RDD and control groups in the left hippocampus ($P = .045$), right hippocampus ($P = .001$), and right lentiform nucleus ($P = .049$).

Conclusion: This study revealed alterations of regional perfusion in the brains of patients with RDD that differed from those in patients with NDD. These results are consistent with the concept that RDD is associated with decreased activity of the bilateral prefrontal areas; and NDD, with decreased activity of left frontal areas in conjunction with overactivity of the bilateral limbic system.

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Despite substantial advances in the treatment of patients with depressive disorders, approximately 30% of these patients do not respond to standard antidepressant treatment. Nonresponders are classified as having refractory depressive disorder (RDD), and responders are said to have nonrefractory depressive disorder (NDD) (1). Studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) have found abnormal regional cerebral blood flow (rCBF) (2–8), though results were inconsistent. These contradictory findings suggest a complex neuropathophysiology in depressive disorder, which may relate to differences in disease development and treatment response. This prompted us to investigate cerebral blood flow in two clinically relevant subtypes of depression, RDD and NDD, in the hope that noninvasive measurements might eventually make it possible to distinguish between these two groups at an early stage.

We chose arterial spin-labeling (ASL) magnetic resonance (MR) imaging, a noninvasive technique for quantifying regional brain perfusion (9). In comparison to PET and SPECT, ASL MR imaging has the advantage of not using radioactive sources. Unlike other MR methods, ASL does not involve injection of a contrast agent. Both advantages are important if these measurements are to be useful in tracking therapeutic effect. ASL MR imaging has been used in both healthy subjects and patients (10–14). Our purpose was to apply ASL MR imaging to quantitatively compare focal cerebral perfusion between patients with RDD, patients with NDD, and healthy control subjects.

Advances in Knowledge

- This study provides neuroimaging evidence to suggest differing focal alterations in cerebral perfusion between patients with refractory depressive disorder (RDD), patients with nonrefractory depressive disorder (NDD), and control subjects.
- By using the noninvasive MR imaging technique of arterial spin labeling (ASL), our study revealed abnormal cerebral perfusion in a large sample ($n = 61$) of patients with depressive disorder.
- Both voxel-based and region-of-interest analyses provided convergent evidence of perfusion differences, suggesting a different role for the limbic system in RDD versus NDD.

Materials and Methods

Participants

This study was approved by the local ethical committee, and written informed consent was obtained from all participants. The patients were part of a large cohort study of major depression in people of Han descent in the Chinese population. Patients were consecutively recruited, and the diagnosis of depression was made according to the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, (15). Exclusion criteria included age younger than 18 years, age greater than 60 years, bipolar disorder, history of major illness, previous psychiatric therapy, cardiovascular disease, vasoactive medications, and alcohol or drug abuse. Of 75 right-handed patients recruited, 14 were excluded on the basis of these criteria. That left 61 patients for our analysis, none of whom had received antidepressant treatment before enrollment. Severity of depression was quantified by using the 17-item Hamilton Rating Scale for Depression (HRSD) (16) and the Clinical Global Impression of Severity scale (17). Inclusion criteria included an HRSD total score greater than or equal to 18 and a Clinical Global Impression of Severity score greater than or equal to four on the day of the MR examination.

Following MR imaging, patients were treated with antidepressants. Three classes of antidepressants were used: tricyclic, typical serotonin-norepinephrine reuptake inhibitor, and typical selective serotonin reuptake inhibitor. All antidepressants were empirically applied. RDD has been defined as a poor response after at least two trials with antidepressants from different pharmacologic classes, for which dosage, duration (6 weeks each), and compliance were adequate (18,19). We defined a poor response as a less than 50% reduction in HRSD score, which was chosen to permit straightforward analysis and clinically relevant interpretation.

Forty-two right-handed healthy control subjects were recruited from the local area by using poster advertisements. Control subjects were screened by using the Nonpatient Version Structured Interview from the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, to confirm the absence of a history of

Implications for Patient Care

- Understanding the different neurophysiologic flow patterns underlying RDD and NDD has the potential to aid clinicians in selecting treatment for particular patient subgroups.
- ASL provides a quantitative measure of baseline perfusion to study the underlying mechanism of depression.
- ASL might also be of value in future research to monitor the effect of antidepressants.

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Abbreviations:
ASL = arterial spin labeling
HRSD = Hamilton Rating Scale for Depression
NDD = nonrefractory depressive disorder
rCBF = regional cerebral blood flow
RDD = refractory depressive disorder
ROI = region of interest

Author contributions:
Guarantors of integrity of entire study, X.H., K.Z., Q.Y.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, S.L., X.H., K.Z., R.C.K.C., L.Z., D.L., H.T., T.Z., X.L., Y.W., X.S.; clinical studies, S.L., L.M.P., X.H., K.Z., H.Y., D.L., H.T., T.Z., X.L., Y.W., L.C., X.S.; statistical analysis, S.L., L.M.P., K.Z.; and manuscript editing, S.L., L.M.P., X.H., K.Z., R.C.K.C., G.J.K.

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psychiatric or neurologic illness and were interviewed to exclude those subjects with a family history of psychiatric illness. All participants were reported to have no abnormalities on conventional MR images by two experienced radiologists (H.Y. and T.Z., with 13 and 10 years experience, respectively, in neuroimaging).

MR Imaging

From February 2006 to July 2007, control subjects and patients were imaged by using a 3-T MR system (Excite; GE Healthcare, Milwaukee, Wis) with an 8-channel phased-array head coil. Patients were imaged before commencement of treatment. During the MR examination, participants were instructed to relax with their eyes closed but without falling asleep, which was confirmed after completion. Participants were fitted with soft ear plugs and were positioned carefully in the coil with comfortable support. ASL MR imaging was performed by using a flow-sensitive alternating inversion-recovery sequence with the following parameters: repetition time msec/echo time msec/inversion time msec, 3900/11.3/1400; delay from end of echo-planar acquisition to next labeling pulse, 2000 msec; section thickness, 5 mm; 10 sections; 64 signals acquired (32 interleaved label); matrix, 64 × 64; field of view, 240 mm; voxel size, 3.75 × 3.75 × 5 mm. The section-selective inversion pulse extended 10 mm beyond the section coverage to avoid any artifacts due to an imperfect edge profile of the inversion. This procedure was repeated twice to allow full coverage of the brain. For voxel-based analysis, a standard echo-planar sequence (repetition time msec/echo time msec, 2000/30; flip angle, 90°; matrix, 64 × 64; field of view, 240 mm) was used with the same section thickness and coverage as the flow-sensitive alternating inversion-recovery sequence.

Data Processing and Analysis

The ASL images (the first two images were excluded from analysis to avoid T1 equilibrium effects) were subtracted and averaged to give perfusion-weighted images. Quantitative perfusion maps were produced (L.M.P., with 10 years experience in MR physics) by using a single-blood-compartment model (20). The equilibrium magnetization of arterial blood was estimated from the average signal intensity on the echo-planar image, assuming a whole-brain value of 0.9 for the brain-to-blood partition coefficient (λ) (21). After correcting for the different T2* relaxation times of blood and tissue (22), perfusion maps were produced by using an equation adapted from an article by Parkes and Tofts (20):

$$f = \frac{S\lambda e^{\frac{TI}{T1_b}} e^{\left(\frac{TE}{T2_b^*} - \frac{TE}{T2_t^*}\right)}}{2S_0 \cdot TI},$$

where f is perfusion, S is signal intensity on the perfusion-weighted image, TI is

Table 1

Demographic Information and Disease Severity by Participant Group

Variable	Patients		*P* Value*	Control Subjects	*P* Value†
	NDD ($n = 37$)	RDD ($n = 24$)		($n = 42$)	
Woman-to-man ratio	11:26	8:16	.7	15:27	.6
Age (y)	33 ± 12 (18–59)‡	35 ± 12 (18–60)‡	.4	37 ± 13 (16–58)‡	.3
Disease duration (mo)	24 ± 21§	192 ± 118§	.01	. . .	. . .
HRSD score	24 ± 4§	22 ± 4§	.6	. . .	. . .

* *P* value for NDD versus RDD.

† *P* value for all patients (NDD and RDD) versus control group.

‡ Data are mean ± standard deviation, with range in parentheses.

§ Data are mean ± standard deviation.

Figure 1

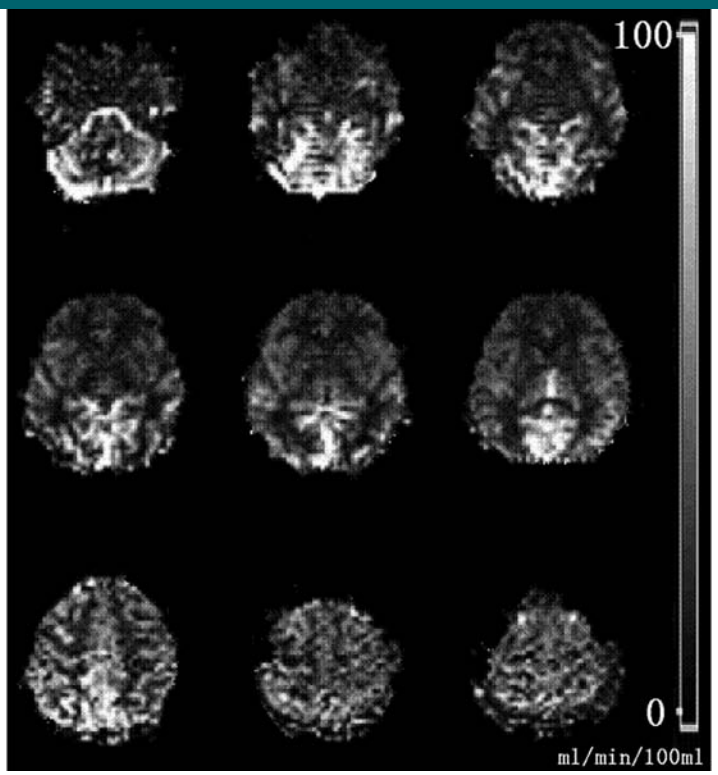


Figure 1: Perfusion map of 35-year-old man randomly selected from the control group. Voxel size was 3.75 × 3.75 × 5 mm, and value of each voxel represents cerebral blood flow.

inversion time, $T1_b$ is T1 of blood, TE is echo time, $T2_b^*$ is approximate T2* of blood, $T2_t^*$ is approximate T2* of tissue, and S_0 is whole-brain equilibrium tissue magnetization. The value used for $T1_b$ was 1.6 seconds (23); that for $T2_b^*$, 100 msec (24); and that for $T2_t^*$, 50 msec (24). The value used for $T2_b^*$ is only approximate owing to the difficulties in measuring this quantity in vivo. Previous research (10) obtained a value of 73 msec for arterial blood ex vivo, which represents a lower limit. S_0 was calculated from the average signal intensity on the ASL control image (S_c), following correction for inversion time, by using the equation

$$S_c = S_0\left(1 - 2e^{\frac{-\mathrm{TI}}{T1}}\right),$$

where T1 is an approximate whole-brain value for T1. The value used was 1 second, which was determined on the basis of values for cortical gray matter (1290 milliseconds) and white matter (830 milliseconds) in the literature (24).

Image preprocessing and statistical analysis were carried out by three of the coauthors (S.L., T.Z., and X.L., with 6, 10, and 3 years experience in MR research, respectively) with software (SPM2; Wellcome Department of Imaging Neuroscience, *http://www.fil.ion.ucl.ac.uk*). For each participant, echo-planar images were spatially normalized to the Montreal Neurological Institute echo-planar image template in SPM2. Then, the parameters were applied to the corresponding perfusion maps and each voxel resampled to $3 \times 3 \times 3$ mm. Finally, images were spatially smoothed by using an isotropic Gaussian filter (8-mm full-width half-maximum) (25).

Statistical Analysis

For all analyses, a *P* value less than .05 with family-wise error correction was considered to indicate a significant difference.

Effects of age and sex between the patient and control groups were analyzed (S.L.) by using a design model of one-way analysis of variance. The two-sample *t* test was used to compare depression severity (HRSD score) and disease duration between the RDD and NDD groups.

Voxel-based comparison of perfusion maps between the three groups was performed by using a design model of one-way analysis of variance, with post hoc analysis that used age and disease duration as covariates. The significance of each region was estimated by distributional approximations from the theory of random Gaussian fields (26): Clusters in smooth areas are shrunken, while clusters in rough areas are expanded to account for differences in smoothness (26). For the hippocampus, putamen, and thalamus, which are believed to be important in mood modulation, small-volume correction in SPM2 was used. Small-volume correction was automatically implemented on the basis of a region of interest (ROI) mask that limits the number of statistical comparisons for more robust inference (27). Montreal Neurological Institute coordinates were transformed to Talairach coordinates by using software (MNI2tal; *http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/*). Results are presented by using the voxel of peak significance.

ROI analysis was carried out (S.L.) by using an automated tool (MarsBaR, version 0.38.2; *http://marsbar.sourceforge.net*). Six subcortical areas (ie, bilateral hippocampi, lentiform nuclei, and thalami) belonging to the limbic-striatal-pallidal-thalamic circuit, which is important in mood modulation, were selected for ROI analysis. The perfusion-weighted image was normalized to the Montreal Neurological Institute template, and labeled regional boundaries with different masks (hippocampi, lentiform nuclei, and thalami) were applied by using software (WFU Pickatlas; Wake Forest University, Winston-Salem, NC) (28). Then regional values were extracted and analyzed. The normalized perfusion-weighted images with ROI labeling were input into MarsBaR (version 0.38.2) with a design model of one-way analysis of variance with age and disease duration as covari-

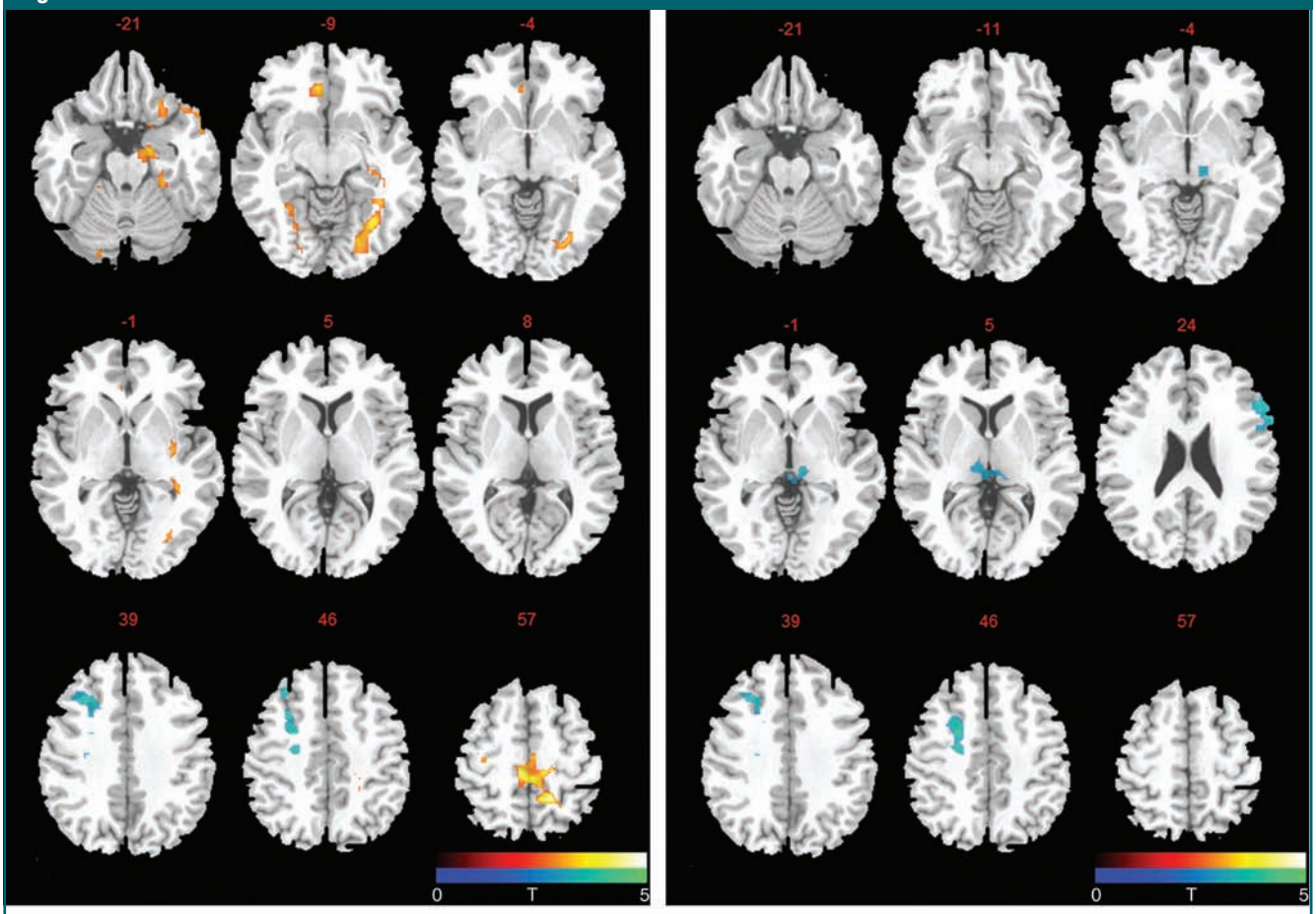
Table 2

Voxel-based Analysis of Global Perfusion Differences between Participant Groups

Difference and Location	Talairach Coordinates			Voxel Size	*P* Value
	x	*y*	*z*		
Control subjects have greater perfusion than patients with NDD					
Left middle frontal gyrus	−30	14	41	154	.0032
Control subjects have greater perfusion than patients with RDD					
Left middle frontal gyrus	−24	5	47	214	.0025
Left occipital lobe	−21	−89	18	182	.0072
Right inferior frontal gyrus	56	16	21	106	.011
Left thalamus	−6	−26	7	46	.015*
Right thalamus	6	−24	1	37	.024*
Patients with NDD have greater perfusion than control subjects					
Right occipital lobe	30	−61	−4	319	.0029
Left occipital lobe	−21	−82	−9	140	.032
Right lentiform nucleus	30	−12	1	24	.049
Right hippocampus and amygdala	24	−9	−12	109	.042
Paracentral lobule extending to precuneus	15	−44	55	510	<.001
Patients with NDD have greater perfusion than patients with RDD					
Paracentral lobule	3	−29	59	228	.0013
Right occipital lobe	45	−48	−25	573	.00017
Left occipital lobe	−24	−64	−4	209	.042
Right hippocampus	35	−35	−6	40	.024*
Right lentiform nucleus	30	−12	1	255	.049
Left lentiform nucleus	−27	0	−5	78	.003*
Anterior cingulate cortex	3	32	−9	118	.047

* $P < .05$, corrected with small-volume correction.

Figure 2



a. b.

Figure 2: **(a–c)** Voxel-based analysis showing decreased (blue) and increased (red) rCBF. **(a)** Patients with NDD compared with control subjects. **(b)** Patients with RDD compared with control subjects. *(Fig 2 continues.)*

ates, and post hoc analysis was used to find differences between groups.

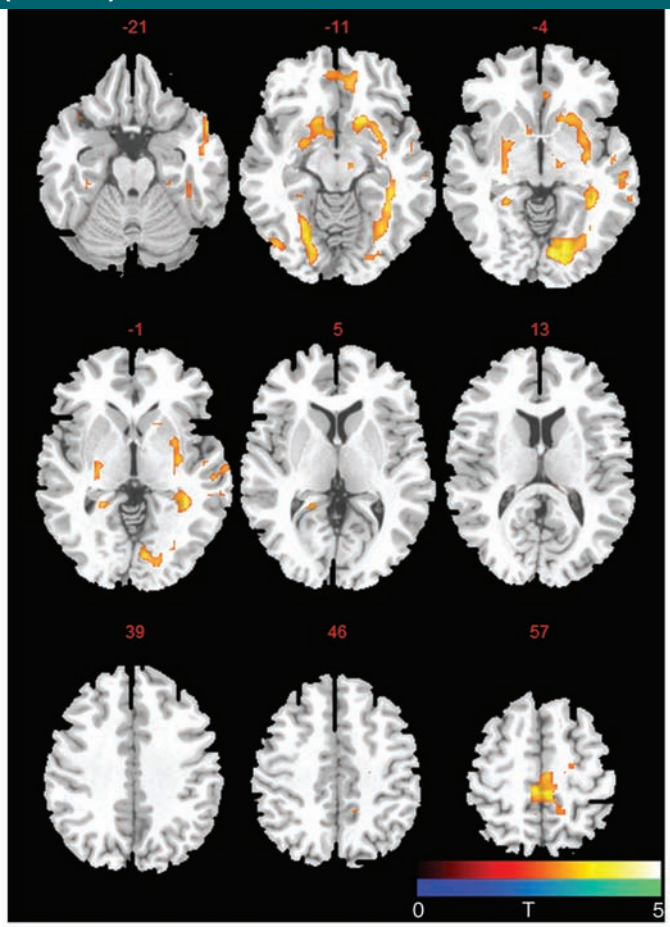
Results

Age and sex were not significantly different between the patient and control groups ($P = .6$ and .3, respectively). Depression severity (HRSD score) was not significantly different between the RDD and NDD groups ($P = .6$), although the RDD group had longer disease duration than did the NDD group (Table 1). Differences in HRSD scores between men and women did not reach statistical significance in either the RDD (men, 22 ± 4; women, 23 ± 4) or NDD (men, 24 ± 4; women, 25 ± 5) groups, and HRSD scores did not correlate with age ($P = .4$). There were no significant differences in global rCBF ($P = .2$), which was 40 mL/min/100 mL ± 9 in the RDD group (men, 39 mL/min/100 mL ± 10; women, 41 mL/min/100 mL ± 7), 41 mL/min/100 mL ± 10 in the NDD group (men, 40 mL/min/100 mL ± 9; women, 41 mL/min/100 mL ± 12), and 42 mL/min/100 mL ± 10 in the control group (men, 43 mL/min/100 mL ± 11; women, 40 mL/min/100 mL ± 9). Global rCBF did not correlate with age in control subjects or patients. An example of a quantitative perfusion map is shown in Figure 1.

Voxel-based Analysis

Compared with control subjects, patients with NDD showed significantly reduced rCBF in the left prefrontal lobe and significantly increased perfusion in the bilateral hippocampi, right lentiform nucleus, paracentral lobule, and left occipital areas (Table 2, Fig 2). In contrast, patients with RDD showed significantly decreased rCBF mainly in the bilateral frontal areas and bilateral thalami, with no areas of significantly increased perfusion (Table 2, Fig 2) compared with control subjects. Though the NDD and RDD groups showed similar hypoperfusion in the left dorsolateral prefrontal area, patients with RDD showed marked hypoperfusion involving the right prefrontal area and bilateral thalami. Notably, only patients with NDD showed hyperperfusion involving limbic-pallidal and temporo-occipital ar-

Figure 2 (continued)



c.

Figure 2 *(continued):* Voxel-based analysis showing decreased (blue) and increased (red) rCBF. **(c)** Patients with NDD compared with patients with RDD. Results were overlaid on the template averaged from all participants. Significance of each region ($P < .05$) was estimated by distributional approximations from the theory of random Gaussian fields.

eas. Direct comparison between the NDD and RDD groups also showed higher perfusion in the bilateral hippocampi, lentiform nucleus, occipital lobes, paracentral lobule, and anterior cingulate cortex in patients with NDD than in those with RDD. This did not correlate with disease duration or age.

ROI Analysis

The NDD group showed significantly higher rCBF than both the RDD and control groups in the left hippocampus (NDD, 22 mL/min/100 mL ± 6 [men, 22 mL/min/100 mL ± 5; women, 22 mL/min/100 mL ± 8]; RDD, 19 mL/min/100 mL ± 7 [men, 18 mL/min/100 mL ± 7; women, 20 mL/min/100 mL ± 8]; control, 19 mL/min/100 mL ± 6 [men, 19 mL/min/100 mL ± 5; women, 20 mL/min/100 mL ± 8]; $P = .045$), in the right hippocampus (NDD, 25 mL/min/100 mL ± 7 [men, 24 mL/min/100 mL ± 5; women, 25 mL/min/100 mL ± 10]; RDD, 20 mL/min/100 mL ± 6 [men, 19 mL/min/100 mL ± 5; women, 21 mL/min/100 mL ± 8]; control, 20 mL/min/100 mL ± 5 [men, 20 mL/min/100 mL ± 7; women, 18 mL/min/100 mL ± 8]; $P = .001$), and in the right lentiform nucleus (NDD, 21 mL/min/100 mL ± 7 [men, 22 mL/min/100 mL ± 9; women, 20 mL/min/100 mL ± 7]; RDD, 18 mL/min/100 mL ± 6 [men, 18 mL/min/100 mL ± 4; women, 19 mL/min/100 mL ± 8]; control, 19 mL/min/100 mL ± 7 [men, 20 mL/min/100 mL ± 6; women, 19 mL/min/100 mL ± 9]; $P = .049$) (Fig 3). Differences between the NDD, RDD, and control groups did not reach statistical significance in the left lentiform nucleus (NDD, 19 mL/min/100 mL ± 7; RDD, 17 mL/min/100 mL ± 6; control, 18 mL/min/100 mL ± 7; $P = .28$) or in the bilateral thalami (left thalamus, $P = .11$; right thalamus, $P = .079$) (Fig 3).

Discussion

By using ASL in a large cohort of patients with well-characterized depression who were studied before commencement of medication, altered rCBF was shown to mainly involve the frontal-subcortical circuits, which are strongly implicated in depressive disorder (29). Moreover, we have shown differences in perfusion abnormalities between NDD and RDD. Patients with NDD showed decreased perfusion in the left prefrontal cortex (part of the limbic-thalamo-cortical circuit) and increased perfusion in the bilateral hippocampi, right lentiform nucleus, and left occipital areas (parts of the limbic-striatal-pallidal-thalamic circuit). By contrast, patients with RDD mainly showed decreased perfusion in the bilateral frontal areas and bilateral thalami (parts of the limbic-thalamo-cortical circuit).

Our observation of frontal hypoperfusion in depression is consistent with the reported decrease in glutamate, glutamine, and γ-aminobutyric acid levels (30). This frontal hypoperfusion might be due to reduced frontal neuronal size and glial cell density (31) or abnormal vascular factors (32), such as ICAM-1 (a marker of ischemia-induced inflammation) (33). If, as has been argued (34), metabolism in the prefrontal and thalamic areas relates to the production of "normal" emotion, hypometabolism and hypoperfusion in these areas is at least consistent with abnormal production of emotion in depression. This is supported by neuropsychological evidence that lesions of the frontal cortex result in depressive symptoms (35). Addition-

ally, reports (36,37) of increased perfusion or metabolism in the dorsolateral prefrontal and thalamic areas after antidepressant therapy in well-responding patients agree with our observations.

Interestingly, the RDD group showed more areas of hypoperfusion compared with the control group than did the NDD group in the right prefrontal area and bilateral thalami. More severe frontal hypoperfusion has also been reported in late-onset depression that is associated with frontal vascular disease (32), and these patients showed higher rehospitalization rates and treatment resistance (38). Though the cause of frontal hypoperfusion in RDD is still unclear, therapeutic intervention targeted at frontal areas has been reported to be useful in patients with RDD (36,39) and is correlated with their clinical improvement (40). Our findings may explain some of the contradictory results (2,41) obtained from possibly inhomogeneous patient groups, namely different proportions of RDD and NDD patients.

Compared with control subjects and patients with RDD, patients with NDD showed higher perfusion mainly in the limbic-striatal-pallidal-thalamic circuit, which is important in modulating emotion. Hyperactivity in the limbic areas, lentiform, and temporo-occipital cortex has also been reported to be associated with experiencing sad events (42) or unpleasant stimuli (34). Our results are consistent with previous reports (13,14,43,44) of decreased perfusion or metabolism in the limbic and striatal areas after successful antidepressant therapy. Among these studies, Clark et al (13,14) used ASL MR to find greater perfusion in the anterior cingulate cortex and right amygdala in responders to partial sleep deprivation ($n = 5$) than in nonresponders ($n = 12$).

Our study provides evidence of different neuropathophysiology in RDD and NDD, which had been suggested in previous studies (13,14,45). It is likely that RDD is associated with decreased activity in bilateral frontal areas, while NDD is mainly associated with increased activity in bilateral limbic-pallidal and temporo-occipital areas and decreased activity in the left frontal areas.

Figure 3

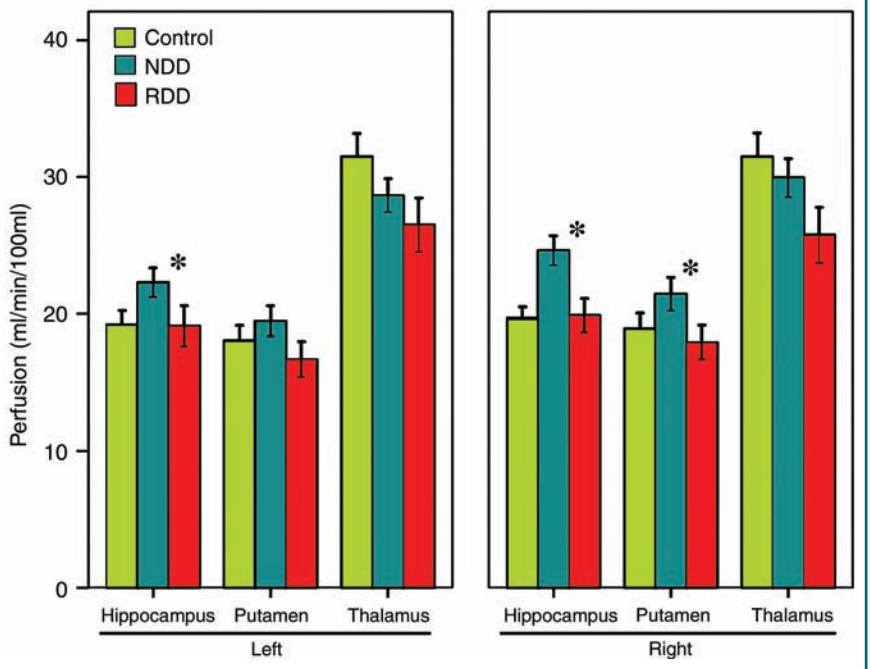


Figure 3: Bar graph of ROI analysis in bilateral hippocampi, lentiform nuclei *(Putamen)*, and thalami between control, NDD, and RDD groups. Values are means with standard error of the mean bars. NDD group showed significantly increased rCBF (*) ($P < .05$) compared with control and RDD groups in bilateral hippocampi and right lentiform nucleus. RDD group showed no difference ($P > .05$) from control group in these areas.

The limbic system has widespread connections to the prefrontal cortex, amygdala, and thalamus (46) and, in addition to its contribution to learning and memory, plays a critical role in anxiety and depressive states (47). Overactivity of the limbic areas in NDD might conceivably stimulate the hypothalamic-pituitary-adrenal axis (48,49), and glucocorticoid oversecretion could be partially responsible for frontal lobe integrity (50).

In addition, high levels of glucocorticoids can reduce serotonin receptors in the hippocampus and other areas (51), and such a reduction is reported in the frontal and limbic areas in depression (52). Most antidepressants target serotonin receptors that are decreased, mainly in the limbic system (51), and patients with NDD show decreased perfusion mainly in the hippocampus and lentiform nucleus (44).

Taking these reports together with our present findings, we suggest that NDD is mainly associated with overactivity in the bilateral limbic-pallidal areas, which are the target of standard antidepressants, while RDD is associated with decreased activity in the bilateral frontal areas, which are not the main target. This may partly explain why patients with RDD are refractory to standard antidepressants but respond well to treatments targeted at the frontal areas (36,39,40).

Some limitations must be addressed. The RDD group was smaller than both the NDD and control groups, which may have reduced the sensitivity to effects in the RDD group. However, the results of both voxel-based and ROI analysis cohered. We also assumed a single blood compartment (20) to quantify perfusion. In favor of this approach, our global perfusion values of 40 mL/min/100 mL are in reasonable agreement with those in previous studies (9,53) that used both non-ASL and ASL techniques. Nevertheless, although assuming that labeled water remains intravascular during the inversion time simpli-

fies calculation, it may underestimate perfusion. The relatively long inversion time of 1400 msec was chosen to allow signal intensity from larger vessels to flow through the image section to reduce contamination by arterial blood destined to perfuse tissue downstream. Although this relatively long inversion time reduces the effect of blood transit time on the ASL signal (54), it will not necessarily eliminate any transit time effects that are not accounted for by nonsignificant differences in age and sex and does not exclude cerebrovascular disease. A more rigorous approach (eg, quantitative imaging of perfusion using a single subtraction–type modification to the sequence) could help to clarify this in future studies.

In summary, in our study using ASL MR imaging in a relatively large cohort (n = 61) of patients with depressive disorder that was well-characterized with respect to severity and treatment response, results were strongly suggestive of different cerebral perfusion patterns in NDD versus RDD. These differences might be useful in diagnosis and therapeutic planning in the two subtypes of patients. Although the groups were not statistically different for depression severity, age, sex, or handedness, there are other possible confounding variables (eg, disease duration was longer in RDD than in NDD, longer treatment with antidepressants might conceivably have an impact on cerebral perfusion [44,55]). Resolving this will require studying a larger cohort both before and after antidepressant therapy.

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