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Supplement DS1

Details of the 6-week SSRI treatment trial

Patients were assessed four times by HDRS-17 and YMRS across a 6-week period, including at baseline and at the end of weeks 2, 4, and 6, after the initiation of antidepressant treatment. Patients had severity scores >= 15 on the HDRS-17 at baseline. Due to ethical considerations, only patients free from medication treatment for at least one month were recruited for this open trial. One of the serotonin-specific reuptake inhibitors (SSRI, including citalopram, escitalopram, or sertraline) was selected based on clinical judgment and started the morning after the baseline assessment. The initial dose was 10mg/day for citalopram, 5mg/day for escitalopram, and 25mg/day for sertraline; all were subsequently increased to the target dose (citalopram: 20mg/day, escitalopram: 10mg/day, and sertraline: 50 mg/day) in 2 weeks. The protocol allowed the dose to be increased to twice the target dose based on clinical response. These doses are in the labeled range for the prescribed SSRIs. If patients presented with prominent anxiety and insomnia, benzodiazepine was permitted, but use was limited to a range of 2 mg/day lorazepam equivalent during the 6-week trial.

Imaging studies

Magnetic resonance imaging (MRI) data acquisition

T1-weighted images (T1-images) were acquired mainly for improving spatial registration and normalization of PET data, on a 3T MR system (GE Discovery 750 whole-body high-speed imaging device). Head stabilization was achieved with cushioning, and all of the participants wore earplugs (29 dB rating) to attenuate the noise. Automated shimming procedures were performed, and scout images were obtained. A high-resolution structural image was acquired in the sagittal plane using a high-resolution sequence (repetition time [TR]=2530 ms, echo spacing=7.25 ms, echo time [TE]=3 ms, flip angle=7°) and an isotropic 1-mm voxel (FOV 256x256).

Positron emission tomography (PET) data acquisition

PET scans of glucose utilization were acquired on a PET/CT scanner (Discovery VCT; GE Healthcare, USA) with a 3D brain mode. Patients fasted for at least 4 h before the PET examination. PET images were acquired in the 45 minutes following an intravenous injection of about 370 MBq of ^{18}F-FDG. The brain acquisition time was 15 minutes. The system produces 47 consecutive slices over an axial length of 15.7 cm, with a slice thickness of 3.75 mm and a transaxial FOV of 70 cm. PET images were reconstructed in a 128×128 matrix, and corrected for attenuation using CT information with the ordered-subset expectation maximization iterative reconstruction algorithm (6 iterations and 14 subsets). Then the axial images were realigned to yield sagittal and coronal images.

Table DS1 Comparison of glucose metabolism among MRD and non-MRD patients and healthy controls (HCs)

Anatomical regions	Brodmann area	Cluster size	Coordinate			F/t	Z	$P_{corrected}$
			x	y	z			
Three group comparisons						**F-value**		***P*[a]**
Left middle temporal gyrus	21	2436	-60	-26	-14	25.21	5.36	0.001
	20		-56	-46	-12	21.94	5.07	0.005
Left dorsolateral PFC	9	7157	-20	32	42	20.11	4.88	0.011
	9		-36	22	38	18.58	4.71	0.022
	8		-4	38	48	14.24	4.17	0.046
Right dorsolateral PFC	9		34	30	34	18.09	4.66	0.024
	8		8	30	52	18.58	4.71	0.022
Supplementary motor area	6		-40	4	44	21.11	5.08	0.005
	6		46	42	48	17.35	4.52	0.032
MRD < non-MRD						**t-value**		***P*[b]**
Left dorsolateral PFC	9	4306	-20	32	42	4.64	4.02	0.004
	8		8	32	52	4.80	4.14	0.001
Right dorsolateral PFC	9		34	32	38	4.76	4.11	0.002
Supplementary motor area	6		-2	16	64	4.71	4.05	0.002
MRD < HC								
Left middle temporal gyrus	21	1694	-60	-24	-14	6.44	5.41	0.000
	20		-56	-48	-10	5.96	5.10	0.000
Right dorsolateral PFC	9	7129	34	30	34	6.01	5.14	0.000
Left dorsolateral PFC	9		-36	22	38	5.99	5.12	0.000
Supplementary motor area	6		-40	4	44	6.25	5.29	0.000
Non-MRD < HC								
Left middle temporal gyrus	20	1809	-56	-30	-14	6.09	5.19	0.000
	20		-56	-42	-14	5.97	5.11	0.000
MRD > non-MRD								
—								
MRD > HC								
—								
Non-MRD > HC								
—								

*Note:*MRD, medication-resistant depression; HC, healthy control subjects; PFC, prefrontal cortex

[a] Results of ANCOVA (adjusted to age, gender and global uptakes); Voxel-level, FWE-corrected for multiple comparisons

[b] Results of independent t-tests, post-hoc searching for brain regions identified in the 3-group comparison; Voxel-level, $p<0.0167$ (0.05/3, corrected for 3 groups).

Table DS2 Correlation of attentional performance to prefrontal glucose metabolism separately in MRD and non-MRD patients and in healthy control subjects

		Go/No-Go			
		Median	Omission	S.D	Mean
PFC rCMglu	**HC**	**- 0.488**†	- 0.041	- 0.074	**- 0.494***
		(0.052)	(0.880)	(0.787)	**(0.048)**
	Non-MRD	- 0.282	- 0.038	- 0.018	**- 0.471**†
		(0.298)	(0.890)	(0.950)	**(0.067)**
	MRD	**-0.356**†	0.248	-0.217	**-0.373**†
		(0.094)	(0.266)	(0.332)	**(0.087)**

Note. Median, Median of reaction time; SD, standard deviation of reaction time

All data processed by Pearson's correlation test and presented as correlation coefficients (p-value)

*P <0.05; $^{\dagger}P$ <0.095

Fig. DS1 Decreased glucose metabolism in medication-resistant depressed (MRD) patients and non-MRD patients vs. healthy control subjects (HC).

Panel A. Non-MRD patients vs. HC. Non-MRD patients demonstrate lower glucose metabolism in the left middle temporal gyrus, compared to healthy control subjects.

Panel B. MRD patients vs. HC. MRD patients had lower glucose metabolism in the left middle temporal gyrus, as well as the dorsolateral prefrontal cortex (DLPFC) and supplementary motor area (SMA) bilaterally, than did healthy control subjects. The color bars (yellow-red) denote *t* value. R, Right; L, Left; B, Bottom; T, Top.

Thresholded at voxel-level corrected *p* value of 0.0167.

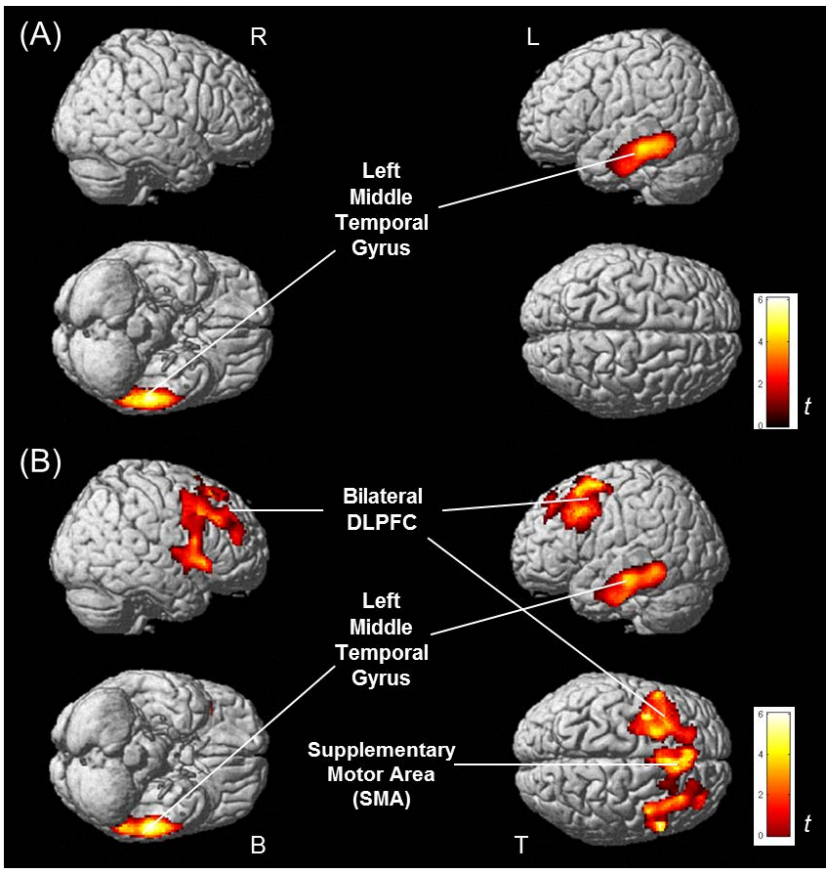

Fig. DS2 Normalized glucose metabolism in some non-a priori brain regions of interest (ROI), including subregions of the PFC (i.e., dorsolateral PFC, DLPFC; ventrolateral PFC, VLPFC; ventromedial PFC, VMPFC; and medial PFC, mPFC), anterior cingulate cortex (ACC), and amygdala (AMG). Mean brain glucose uptake values in these ROI were also extracted from unsmoothed PET images in the standard stereotactic space by using PMOD version 3.0 (PMOD Technologies, Zurich, Switzerland) and normalized glucose uptakes in these ROI (values were normalized by dividing the ROI uptake values by the global mean uptake values) were reported. The most significant region between groups was the bilateral DLPFC [left: $F(2, 51)=4.664$, $p=0.011$ (post-hoc analysis: MRD<non-MRD, MRD<HC), right, $F(2,51)=5.782$, $p=0.005$ (post-hoc analysis: MRD<HC)]. MRD, Medication-Resistant Depression. HC, Healthy Control subjects.

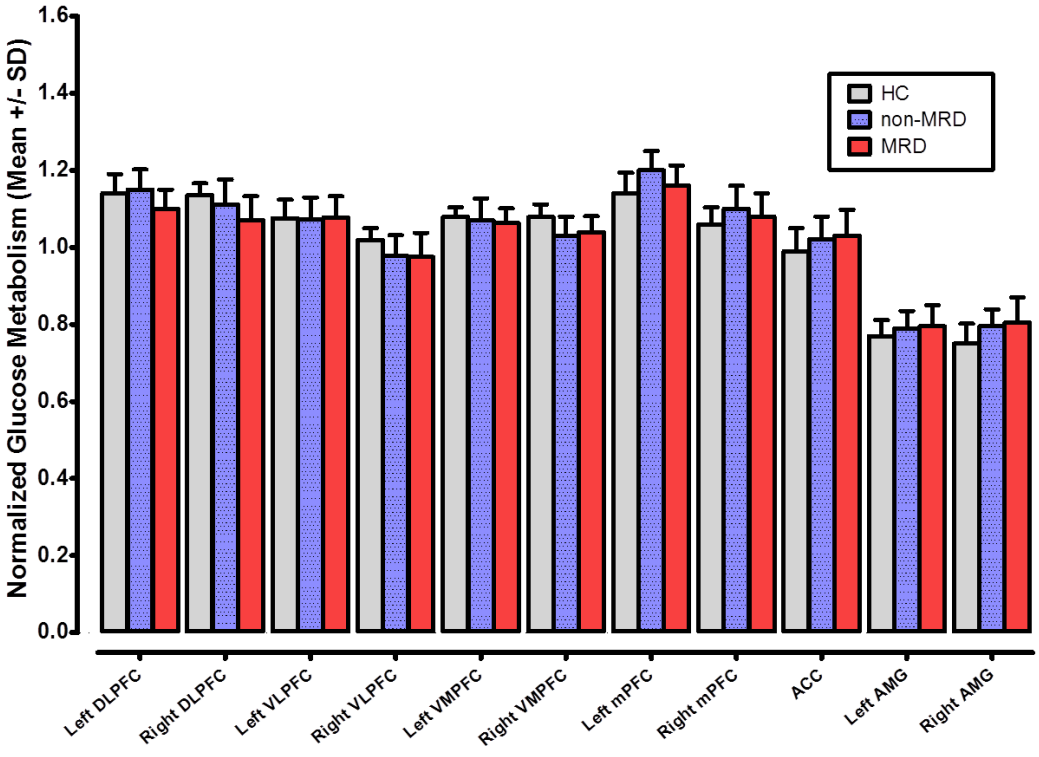

Fig. DS3 Intermediate level-to-treat (ITT, shown in green) patients before the initiation of the 6-week SSRI antidepressant treatment had no significant decrease of rCMglu in the prefrontal cortex compared to the other 3 groups. MRD, medication-resistant depression.

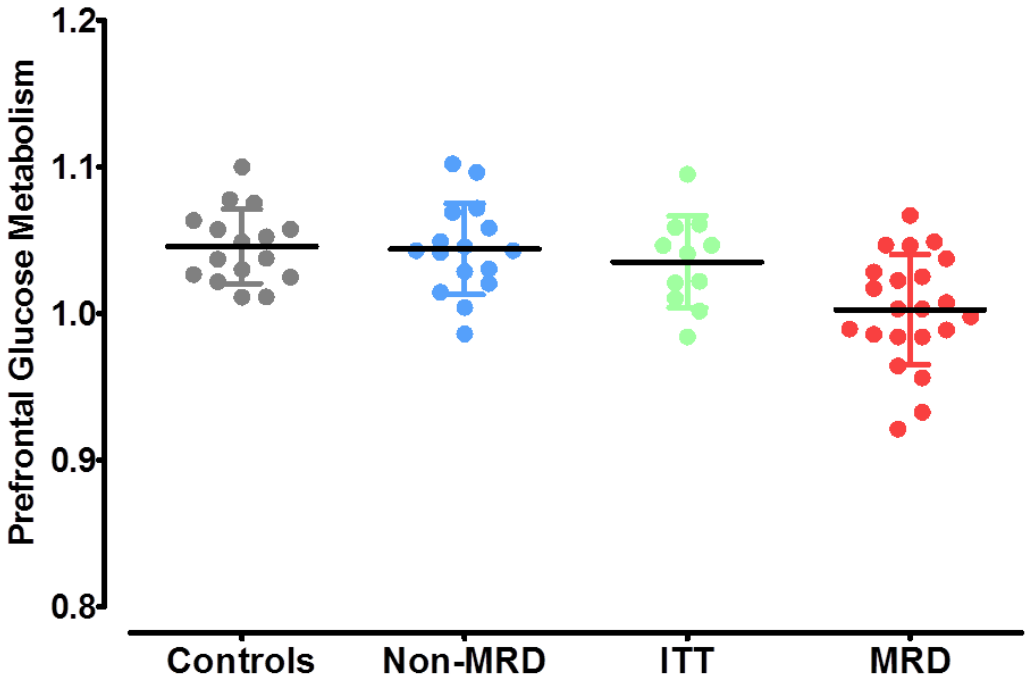

Fig. DS4 Receiver operating characteristic curve (blue line) for assessing the accuracy of prediction of antidepressant treatment outcome by normalized PFC glucose uptake at baseline. Diagonal reference line is shown in green.