Supplementary Online Content

Moriguchi S, Wilson AA, Miler LJ, et al. Monoamine oxidase B total distribution volume in the prefrontal cortex of major depressive disorder: an [^{11}C]SL2511.88 positron emission tomography study. *JAMA Psychiatry*. Published online March 6, 2019. doi:10.1001/jamapsychiatry.2019.0044

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods, Results, and Discussion

I. eMethods

Participants

All participants had negative urine drug and cotinine screens; and women had a negative urine pregnancy test on the PET scan day. Among the 11 women with MDE, 5 were in follicular phase, 1 was in mid cycle, 3 were in luteal phase and 2 in were in menopause. Among the 10 healthy women 4 were in follicular phase, 5 were in luteal phase and 1 were in menopause. None of the subjects were taking oral contraceptives within the past 2 weeks. There were no significant differences in body mass index, alcohol consumption, level of education and racial back ground between groups (Table 1).

PET and MRI Imaging

For MDD patients, injected radioactivity and the molar activity (specific radioactivity) of the radioligand at the time of injection of [^{11}C]SL25.1188 were 330.0 ± 37.6 MBq and 80.3 ± 47.6 GBq/μmol, respectively. For healthy controls, injected radioactivity and the molar activity of the radioligand at the time of injection of [^{11}C]SL25.1188 were 348.2 ± 28.8 MBq and 81.4 ± 43.9 GBq/μmol, respectively. There were no significant differences in the injected dose or molar activity of [^{11}C]SL25.1188 between the MDD and healthy controls (t (38) = -1.7, P = .10; t (38) = -.08, P = .94, respectively). Manual and automatic arterial blood sampling (programmable blood sampler model PBS-101; Veenstra Instruments, Joure, Netherlands) was performed to determine radioactivity in whole blood, the ratio of radioactivity in whole blood to radioactivity in plasma and the unmetabolized radioligand in plasma needed to create the input function for the kinetic analysis.[1] The free fraction in plasma was 0.91 ± 0.24 % in the MDD and 1.02 ± 0.37 % in the healthy controls. There was no significant difference between groups (t (38) = -1.2, P = .25). All PET images were corrected for attenuation using a single photon point source, cesium 137 (half-life, 30.2 years; Eγ, 662 keV) and were reconstructed by filtered back-projection algorithm with a HANN filter at Nyquist cutoff frequency.

The MRI were performed on a Discovery MR750 3.0T GE scanner (Milwaukee, WI, USA) equipped with an 8-channel headcoil. 2D axial proton density images were acquired as follows: fast spin echo imaging, echo time/repetition time/echo train length=MinFull/6s/8, receiver BW±15.63 kHz, field of view=22 cm, 256*256 sampling matrix, slice thickness=2mm and a parallel imaging acceleration factor of 2.[1] ROIs were generated based on individual proton density-magnetic resonance images using an in-house imaging pipeline, ROMI as previously described.[2,3]

II. eResults

In exploratory analyses, in MDE, greater PFC MAO-B V_T was associated with higher HDRS severity on the day of PET scanning (ANCOVA, r = .44, $F_{1,18}$ = 4.3, P =.05; eFigure 1), but not with number of MDE. Exploratory analyses applying rmANCOVA with age, sex, body mass index, alcohol consumption, education years or phase of menstrual cycle and regional MAO-B V_T as the dependent variable found no significant relationship. Also, there was no effect of age, sex, body mass index, alcohol consumption, years of education or phase of menstrual cycle on PFC MAO-B V_T.

III.eDiscussion

The regional distribution of difference in MAO-B V_T between MDE and health exhibits the greatest magnitude in the PFC, more specifically the vlPFC; as well as the thalamus. Also, in the cortex, regions that are farther from the vlPFC have a lower difference in MAO-B V_T between MDE and health. In the introduction it was proposed that glucocorticoid induced elevations in MAO-B density through previously identified dysregulations of nuclear transcription factors in the PFC of MDD, like R1 and TIEG2[4,5] would provide a mechanism for greater MAO-B V_T and we speculate that regional specificity of glucocorticoid effects on MAO-B expression could account for regionally

specific differences between MDE and health. Similar regional specificity was demonstrated in a rodent study of dexamethasone administration at brain penetrant doses, which was associated with much greater MAO-B activity in the PFC, but relatively limited effects in the ACC and hippocampus.[6] A region specific effect of glucocorticoids could also account for why differences in MAO-B V_T between MDE and health are found in the PFC, yet not in some other regions such as the temporal cortex, despite the positive correlation with duration of illness in MDE subjects.

In addition, the particular regional distribution of elevated MAO-B V_T in MDE compared to controls may also have implications for dysregulation of monoamines that support euthymic mood. MAO-B metabolizes norepinephrine and dopamine in humans and alpha-methylparatyrosine (AMPT) administration is a tyrosine hydroxylase inhibitor that lowers brain concentration of these particular monoamines. In paradigms of AMPT administered to MDD subjects in remission, induction of depressive symptoms is associated with reduced [^{18}F]FDG uptake within subregions of the prefrontal cortex and/or thalamus.[7,8]

eReferences

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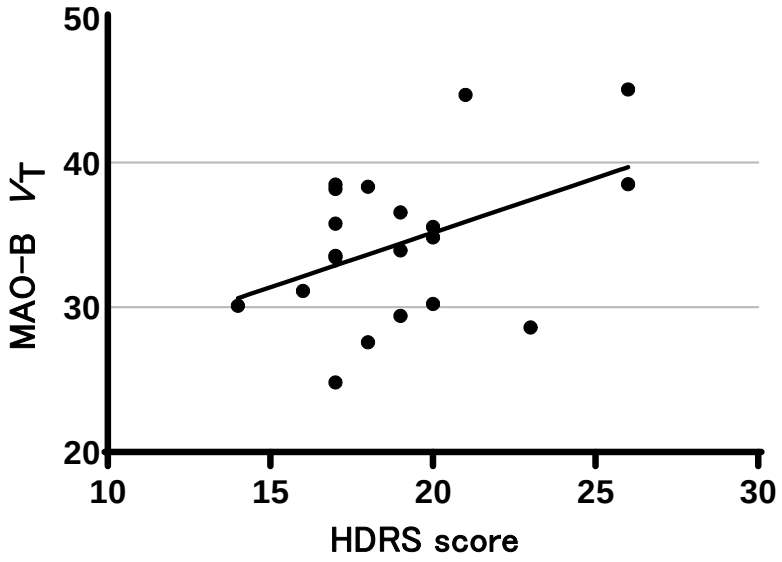
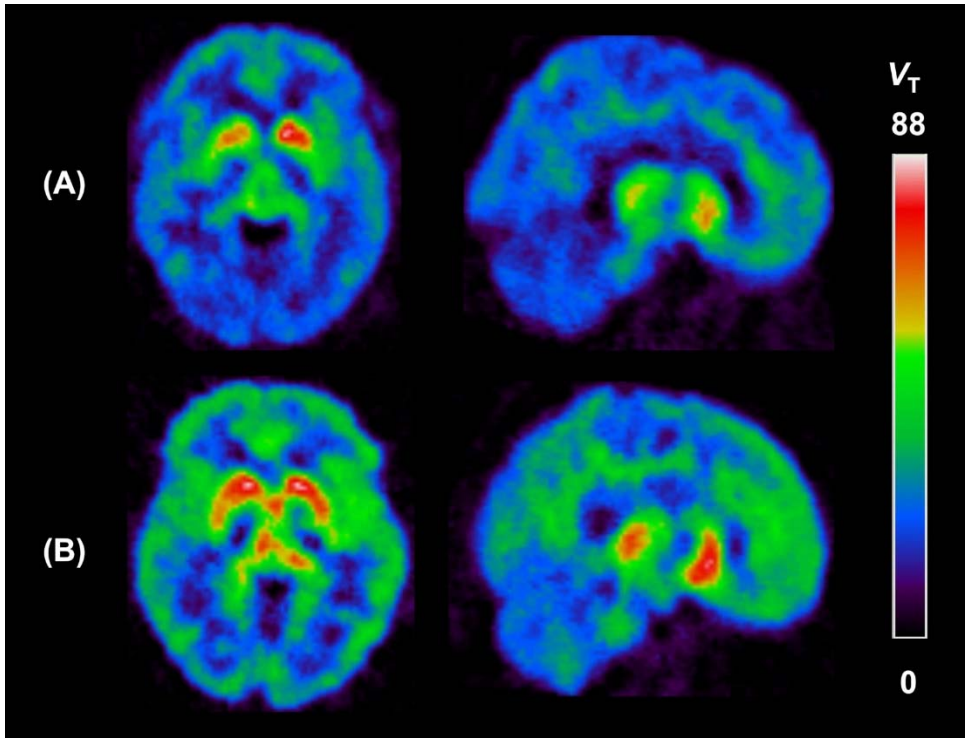
eFigure 1. Relationship Between Prefrontal Cortex MAO-B Distribution Volume and Severity of Major Depressive Episode



Analysis of covariance evaluated MAO-B V_T as the dependent variable and the HDRS score as the covariate (ANCOVA, r = .44, $F_{1,18}$ = 4.3, P =.05; Figure 3).
Abbreviations: MAO-B V_T, monoamine oxidase B density measured by distribution volume; HDRS, 17-item Hamilton Depression Rating Scale.

eFigure 2. Total Distribution Volume in Healthy and Major Depressive Episode Subjects



Two representative participants were chosen with prefrontal cortex [^{11}C]SL25.1188 total distribution volume values similar to the mean of each group. (A) Healthy control (B) Major depressive episode subject

eTable. Analysis of Variance Comparing Regional MAO-B Density and Duration of Major Depressive Disorder[a]

	***r* value**	**$F_{1,18}$ value**	***P* value[b]**
Prefrontal Cortex	.68	15.2	.001
Ventrolateral Prefrontal Cortex	.46	4.8	.042
Dorsolateral Prefrontal Cortex	.65	13.0	.002
Orbitofrontal Cortex	.67	14.9	.001
Medial Prefrontal Cortex	.61	10.5	.005
Anterior Cingulate Cortex	.54	7.6	.013
Ventral Striatum	.09	.15	.70
Dorsal Putamen	.43	4.0	.06
Thalamus	.62	11.1	.004
Inferior Parietal Cortex	.54	7.4	.014
Temporal Cortex	.60	9.9	.006
Occipital Cortex	.50	5.9	.026

[a] Analysis of variance evaluated MAO-B V_T as the dependent variable and duration of illness as the predictor variable
[b] *P* values for correlation ratio and analysis of variance were same values.