Elevated Monoamine Oxidase A Levels in the Brain

An Explanation for the Monoamine Imbalance of Major Depression

Jeffrey H. Meyer, MD, PhD; Nathalie Ginovart, PhD; Anahita Boovariwala, BSc; Sandra Sagrati, BSc; Doug Hussey, BSc; Armando Garcia, BSc; Trevor Young, MD, PhD; Nicole Praschak-Rieder, MD; Alan A. Wilson, PhD; Sylvain Houle, MD, PhD

Context: The monoamine theory of depression proposes that monoamine levels are lowered, but there is no explanation for how monoamine loss occurs. Monoamine oxidase A (MAO-A) is an enzyme that metabolizes monoamines, such as serotonin, norepinephrine, and dopamine.

Objective: To determine whether MAO-A levels in the brain are elevated during untreated depression.

Setting: Tertiary care psychiatric hospital.

Patients: Seventeen healthy and 17 depressed individuals with major depressive disorder that met entry criteria were recruited from the care of general practitioners and psychiatrists. All study participants were otherwise healthy and nonsmoking. Depressed individuals had been medication free for at least 5 months.

Main Outcome Measure: Harmine labeled with carbon 11, a radioligand selective for MAO-A and positron emission tomography, was used to measure MAO-A DVs (specific distribution volume), an index of MAO-A density, in different brain regions (prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, caudate, putamen, thalamus, anterior temporal cortex, midbrain, hippocampus, and parahippocampus).

Results: The MAO-A DVs was highly significantly elevated in every brain region assessed (t test; P = .001 to 3.1 x 10^{-7}). The MAO-A DVs was elevated on average by 34% (2 SDs) throughout the brain during major depression.

Conclusions: The sizable magnitude of this finding and the absence of other compelling explanations for monoamine loss during major depressive episodes led to the conclusion that elevated MAO-A density is the primary monoamine-lowering process during major depression.

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Major depressive disorder is an important illness because it has a 1-year prevalence of 2% to 5% and ranks fourth among causes of death or injury.1 For more than 30 years, it has been theorized that levels of monoamines, such as serotonin, norepinephrine, and dopamine, are generally low in the brain during untreated major depressive episodes (MDEs).2 However, no convincing mechanism of monoamine loss has ever been found.3-11

Previous investigations of monoamine transporters and monoamine synthesis enzymes have not identified a prominent monoamine-lowering process during untreated depressive episodes. Loss of monoamine-releasing neurons is an unlikely mechanism of monoamine loss, since some investigations report no reduction in monoamine transporters and the largest reported reductions in monoamine transporter density indices range from 14% to 25%.3,6,12,13 Even the largest reported reductions in monoamine transporter indices in depression are low compared with monoamine transporter loss observed in symptomatic neurodegenerative disease.14 Moreover, no abnormality in an index of serotonin transporter density was found in vivo in untreated depressed individuals.8 Decreased monoamine synthesis is unlikely during depression because investigations of monoamine synthesis enzymes in monoamine nuclei tend to find no change or modest increases in depressed individuals.9 Studies attempting to determine whether monoamine precursor uptake is reduced in depression are inconclusive because they are typically confounded by recent antidepressant use. Abnormally elevated monoamine oxidase B density seems less likely to occur in depression, as one investigation16 of monoamine oxidase B density in the amygdala found no significant difference in depressed individuals.

Monoamine oxidase A (MAO-A) is a logical enzyme to investigate in depres-
sion because it regulates levels of all 3 major monoamines (serotonin, norepinephrine, and dopamine) in the brain. Whether MAO-A levels in the brain are abnormal during MDEs is unknown because each previous investigation of MAO-A in the brain has had at least 2 critical confounders and/or limitations, including complete nonspecificity of technique for MAO-A vs monoamine oxidase B, enrollment of study participants who had recently taken medication, unclear diagnosis of individuals who committed suicide, small sample size, and lack of differentiation between early-onset depression and late-onset depression. In contrast to the typical, early-onset depression before the age of 40 years, late-onset depression probably has a different pathophysiologic mechanism attributable to lesions and/or degenerative disease.

The MAO-A DV₅₀ (specific distribution volume), an index of MAO-A density, is measurable in vivo in the brain using harmine labeled with carbon 11 ([¹¹C]harmine) positron emission tomography (PET). [¹¹C]Harmine is a selective, reversible PET radiotracer for MAO-A, and MAO-A DV₅₀ is an index of specifically bound [¹¹C]harmine. [¹¹C]Harmine PET demonstrates the requisite properties of a PET radiotracer for measurement of MAO-A: harmine has a high affinity (Ki=2nM) and a selective affinity for the MAO-A enzyme. [¹¹C]Harmine shows high brain uptake in humans with the greatest uptake in regions with the highest MAO-A density. The metabolites of harmine are polar and do not cross the blood-brain barrier. The main advantage of [¹¹C]harmine over clorgyline labeled with carbon 11 ([¹¹C]clorgyline) is that [¹¹C]harmine has reversible brain uptake.

**Figure 1.** Time activity curves for harmine labeled with carbon 11 ([¹¹C]harmine) demonstrating reversible kinetics. Time activity curves for a representative depressed individual (closed circles) and a healthy individual (open circles) are shown. This pair of study participants was chosen because each has monoamine oxidase A (MAO-A) DV₅₀ (an index of MAO-A density) values within 10% of their group mean, and these 2 participants have near identical areas under their [¹¹C]harmine plasma input curves (within 1%).
kinetics, whereas $^{11}$C]clorgyline shows slowly reversible brain kinetics. The main advantage of $^{11}$C]harmine over deuterium-substituted $^{11}$C]clorgyline is that deuterium-substituted $^{11}$C]clorgyline has substantial non–MAO-A binding in humans in some brain regions. The hypothesis of the present study is that the MAO-A DV₃ will be elevated throughout the brain during MDEs in medication-free individuals with major depressive disorder and typical early-onset illness. An elevation in MAO-A density is hypothesized because greater MAO-A could excessively lower brain monoamine levels. The location of elevated MAO-A density was hypothesized to be throughout the brain because monoamine receptor abnormalities in depression consistent with lowered monoamine levels have been reported in several brain regions, including the prefrontal cortex, striatum, and midbrain.

### Table. Sample Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Healthy Group (n = 17)</th>
<th>Depressed Group (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>34 ± 8</td>
<td>34 ± 8</td>
</tr>
<tr>
<td>Women, No.</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Men, No.</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Education, mean ± SD, y</td>
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<td>15 ± 2</td>
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<tr>
<td>Psychiatric diagnosis*</td>
<td>None</td>
<td>Major depressive episode; major depressive disorder</td>
</tr>
<tr>
<td>First major depressive episode</td>
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<td>8</td>
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<td>5</td>
</tr>
<tr>
<td>Third major depressive episode</td>
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<td>4</td>
</tr>
<tr>
<td>No previous antidepressant treatment</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Previous antidepressant treatment†</td>
<td>NA</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*Study participants did not have comorbid Axis I disorders, borderline personality disorder, or antisocial personality disorder.
†No study participant with depression had received antidepressant treatment within the past 5 months.

### METHODS

#### PARTICIPANTS

Twenty individuals with an MDE and major depressive disorder were recruited, and 17 depressed individuals completed the protocol (mean ± SD age, 34.8 years; 8 men and 9 women). Seventeen age-matched healthy individuals were recruited (mean ± SD age, 34 ± 8 years; 10 men and 7 women). Each underwent an $^{11}$C]harmine PET scan. Participants were between 20 and 49 years of age. Healthy participants were age matched within 4 years to depressed patients (Table).

All study participants (MDE and healthy) were physically healthy and nonsmoking and had no history of neurotoxic use. Participants were nonsmoking because it is reported that smoking can lower MAO-A levels, which could create greater variance in measurement. Women in perimenopause or menopause were excluded. Healthy participants were screened to rule out any Axis I disorders, and depressed participants were screened to rule out any comorbid Axis I disorders using the Structured Clinical Interview for DSM-IV. All participants were screened to rule out borderline and antisocial personality disorder using the Structured Clinical Interview for DSM-IV for Axis II disorders. All participants underwent a urine drug screen on the day of the $^{11}$C]harmine PET scan. All depressed patients underwent common blood tests to rule out medical causes of disturbed mood (thyroid function, electrolyte levels, and complete blood cell count).

For depressed patients, the mean ± SD age at onset of illness was 23 ± 10 years. Patients were in their first (n = 8), second (n = 5), or third (n = 4) MDE. No patient with depression had received antidepressant treatment within the past 5 months, and 11 depressed patients had never received antidepressant treatment. For depressed patients, a diagnosis of MDE secondary to major depressive disorder was based on the Structured Clinical Interview for DSM-IV for Axis I disorders and a consultation with a psychiatrist (J.H.M.). For patients with MDE, the minimum severity for enrollment was based on a cutoff score of 17 on the 17-item Hamilton Depression Rating Scale. The mean ± SD Hamilton Depression Rating Scale score for participants with MDE was 22 ± 3. Additional exclusion criteria included MDE with psychotic symptoms, bipolar disorder (type I or II), history of self-harm or suicidality outside episodes of depression, and history of alcohol or other drug abuse.

For each study participant, written consent was obtained after the procedures had been fully explained. The study and recruitment procedures were approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, University of Toronto.

### IMAGE ACQUISITION AND ANALYSIS

A dose of 370 MBq of intravenous $^{11}$C]harmine was administered as a bolus for each PET scan. An automatic blood sampling system was used to measure arterial blood radioactivity continuously for the first 10 minutes. Manual samples were obtained at 5, 10, 15, 20, 30, 45, 60, and 90 minutes. The radioactivity in whole blood and plasma was measured as described previously. Frames were acquired as follows: 15 frames of 1 minute, then 15 frames of 5 minutes. $^{11}$C]Harmine was of high radiochemical purity (>96%; mean ± SD, 98.4% ± 0.8%; n = 34) and high specific activity (mean ± SD, 43 ± 18 terabecquerels/mmol at the time of injection). The PET images were obtained using a GEMS 2048-15B camera (intrinsic in-plane resolution; full width at half maximum, 5.5 mm; Scanditronix Medical, General Electric, Uppsala, Sweden). All images were corrected for attenuation using a germanium 68/gallium 68 transmission scan and reconstructed by filtered back projection using a Hannig filter.

For the region of interest (ROI) method, each participant underwent magnetic resonance imaging (GE Signa 1.5-T scanner; spin-echo sequence, T₁-weighted image: x, y, z voxel dimensions, 0.78, 0.78, and 3 mm, respectively; GE Medical Systems, Milwaukee, Wis). The ROIs were drawn on magnetic resonance images that were coregistered to each summed $^{11}$C]harmine PET image using a mutual information algorithm. The location of the ROI was verified by visual assessment of the ROI on the summed $^{11}$C]harmine PET image. The ROIs were drawn to sample the prefrontal cortex, anterior cingulate cortex, postcentral cingulate cortex, caudate, putamen, thalamus, anterior temporal cortex, midbrain, and a hippocampal and parahippocampal region. The definitions of the ROIs were similar to our previous investigations. The prefrontal cortex regions (left and right) were drawn in transverse planes extending 32.5 mm in the z-axis and included Brodmann areas 9, 10, 46, and part of 8 and 47. The anterior cingulate cortex (Brodmann areas 24 and part of 32) was sampled from adjacent transverse planes extending 26 mm in the z-axis. The putamen and thalamus were drawn within adjacent transverse planes to maximally sample the individual structures. These planes extended 13 mm in the z-axis. The remaining regions were sampled from adjacent transverse planes that extended 19.5 mm in the z-axis. For the temporal cortex, the anterior
third of the temporal cortex was sampled, and this included Brodmann area 38 and part of 20, 21, and 22. The anterior cingulate cortex and the posterior cingulate cortex (part of Brodmann areas 23 and 30) were drawn in transverse planes relative to the corpus callosum.

The kinetics of $^{11}$C-harmine can be described with an unconstrained 2-tissue compartment model (described as method B in our previous publication). Highly identifiable fits with the unconstrained 2-tissue compartment model are obtainable for the DVS. The DVS is an index of specific binding and represents the concentration of the specifically bound radiotracer in tissue relative to plasma concentration at equilibrium. (In previous publications, DVS was referred to as DVB.) The DVS can be expressed in terms of kinetic rate parameters as:

$$DVS = \frac{K_1}{k_2} \times \frac{k_3}{k_4}$$

where $K_1$ and $k_2$ are influx and efflux rates for radiotracer passage across the blood-brain barrier and $k_3$ and $k_4$ describe the radioligand transfer between the free and nonspecific compartment and the specific binding compartment. $K_1/k_2$ is similar among different individuals (for further details see Ginovart et al26).

The $^{11}$C-harmine PET measure of the MAO-A DVS was previously found to be reliable. Under test-retest conditions, for the regions evaluated in this study, the mean absolute difference in MAO-A DVS, expressed as a percentage of MAO-A DVS, ranged from 5% to 17% (n=6 individuals) (J.H.M., A.A.W., S.H., et al, unpublished data, 2005).

### STATISTICAL ANALYSIS

The primary analysis was an independent-sample $t$ test comparing MAO-A DVS between depressed and healthy individuals for each brain region, since it was expected that MAO-A DVS would be significantly elevated in each brain region in the depressed group. We chose to examine each individual region because it would also be of interest whether there were no differences in some brain regions.

As expected, given the previous report of no relationship between age or sex with MAO-A density, there was no relationship between age or sex and regional MAO-A DVS, in our sample (analysis of covariance; effect of age, $F_{1,32}=0.3$ to 0.001; $P=0.50$ to .98; analysis of variance; effect of sex, $F_{1,32}=0.4$ to 0.001; $P=0.50$ to .98).

There was a highly significant elevation in MAO-A DVS in all regions in the depressed group compared with the healthy group (independent-sample $t$ test, $P=0.001$ to <.001; mean difference in MAO-A DVS between groups, 34%; mean effect size, 2) (Figure 2). Because this was not the situation of a single significant finding among a number of nonsignificant findings, a correction for multiple comparisons was not performed. A multiple analysis of variance was also performed, with regional MAO-A DVS as the dependent variable and diagnosis as a predictor variable (effect of diagnosis: $F_{9,24}=5.8$; $P<.001$).

To examine whether MAO-A DVS is related to particular clinical characteristics in addition to diagnosis, secondary post hoc analyses were performed using the Pearson correlation coefficient, correlating regional MAO-A DVS with the following clinical characteristics: duration of illness, episode number, duration of episode, illness severity based on the 17-item Hamilton Depression Rating Scale Score, and lifetime history of antidepressant treatment. None of the correlations reached the trend level ($P<.10$).

### RESULTS

The main finding was that MAO-A DVS, the index of MAO-A density, was elevated on average by 34% (2 SDs). Monoamine oxidase A metabo-
izes all 3 major monoamines (serotonin, norepinephrine, and dopamine) in the brain, and no previous study has convincingly explained why monoamine levels may be low during MDEs; therefore, it is plausible that an elevation in brain MAO-A density is the primary monoamine-lowering process during MDEs.

Elevated brain MAO-A density during MDEs has important implications for the monoamine theory of depression when combined with previous neuroimaging results in medication-free depressed patients (ie, no medication for ≥3 months). An advanced monoamine theory (Figure 3A-D) can be conceptualized: During an MDE, elevated MAO-A levels increase the metabolism of monoamines such as serotonin, norepinephrine, and dopamine. Thereafter, individual monoamine transporter densities have a secondary influence on specific extracellular monoamine levels. If the monoamine transporter density for a particular monoamine is low, the effect of greater monoamine metabolism on extracellular monoamine levels is somewhat attenuated, resulting in a moderate monoamine loss. Long-term, moderate loss of a particular monoamine in specific brain regions eventually results in moderate severity of particular symptoms. If the monoamine transporter density for a particular monoamine is not low during an MDE, then the extracellular concentration of the monoamine is severely reduced and symptoms associated with long-term regional loss of that particular monoamine eventually become severe. In short, elevated MAO-A levels can be viewed as a general monoamine-lowering process (with no relationship to particular symptoms), whereas the regional density of monoamine transporters has a selective influence on particular monoamines (with a strong relationship with particular symptoms).

Data to support this advancement of the monoamine model are found in investigations of drug-free (ie, no medication for ≥3 months), depressed individuals with early-onset depression who do not have comorbid psychiatric or medical illnesses. This includes earlier PET brain imaging studies in addition to the present study. The binding potential (BP) is often measured in PET studies and is an index of receptor density. During MDEs, greater regional serotonin transporter BP is associated with more severely pessimistic thinking (dysfunctional attitudes), and greater striatal dopamine transporter BP is associated with more severe motor retardation. In addition, during MDEs, increased cortex serotonin 2 BP occurs when severe pessimism is present, and increased striatal dopamine 2 BP occurs when severe motor retardation is present. Increased serotonin 2 receptor density can occur when serotonin is lowered in the long term, and increased dopamine 2 BP (as measured with PET with raclopride labeled with carbon 11) can occur when the extracellular dopamine level is low. These studies argue that patients with MDEs and greater monoamine transporter

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Figure 3. Modernization of monoamine theory of depression. A, Description of monoamine release in a synapse in a healthy person. B, During a major depressive episode, monoamine oxidase A (MAO-A) density is elevated, resulting in greater metabolism of monoamines, such as serotonin, norepinephrine, and dopamine, in the brain. C and D, Range of outcomes. If the monoamine transporter density for a particular monoamine is low during a major depressive episode (C), the effect of an elevated MAO-A level on reducing that particular monoamine in the extracellular space is somewhat attenuated, resulting in a moderate loss of monoamine. This eventually results in a moderate severity of symptoms associated with long-term loss of that particular monoamine. If the monoamine transporter density for a particular monoamine is not low during a major depressive episode (D), then there is no protection against the effect of elevated MAO-A levels. The extracellular concentration of the monoamine is severely reduced, and symptoms associated with long-term loss of that particular monoamine eventually become severe. Some postsynaptic receptors increase in density when their endogenous monoamine level is low in the long term. Mostly, MAO-A is found in norepinephrine-releasing neurons but is reported to be detectable in other cells, such as serotonin-releasing neurons and glia. Even so, MAO-A metabolizes serotonin, norepinephrine, and dopamine in vivo.
density are additionally vulnerable to monoamine loss, show up-regulation (or increase in BP) of receptors sensitive to monoamine loss, and have greater severity of particular symptoms.

This advancement in monoamine theory relies on the principle that a single explanation for the findings that directly support it is likely to be the correct explanation. Although one could conceive of different explanations for individual findings, it would be extremely difficult to generate an alternative, single, cohesive explanation for the entire study series. The statistical significance of the comparison of mean regional MAO-A DVs for the current study was $P=3.3 \times 10^{-6}$, and the statistical significances of the previous 4 studies were high ($P=.003$ for elevations in prefrontal serotonin 2 BP in depression with severe pessimistic thinking, $P=.003$ for elevation in striatal dopamine 2 BP for depressed individuals with motor retardation, $P<.001$ for correlation between prefrontal serotonin transporter BP and pessimistic thinking, and $P=.006$ for correlation between striatal dopamine transporter BP and motor retardation). Each study sample was gathered separately. In general, the probability of multiple independent chance events occurring together can be estimated by multiplying the probability of each separate event occurring. For each study, the significance reflects the likelihood of the finding occurring by chance alone. If one took the specific viewpoint that the findings of these studies are unrelated, independent chance events (ie, there is no common model to explain them), then the probability of all of these findings occurring together results in a $P$ value of $2.7 \times 10^{-16}$. Given the resulting statistical significance, it is exceedingly unlikely that these findings represent independent chance events. In addition, the entire sample consisted of 89 depressed and 103 healthy individuals. Depressed patients were drug free for at least 3 months plus 5 half-lives of medication. None had comorbid medical illnesses or Axis I psychiatric illness. 9,8,36,38 and 94% of the sample was nonsmoking. The collective set of highly significant findings in unbiased samples across a series of studies to support a common theory must be considered strongly.

Our monoamine model of depression is consistent with many other findings of monoamine research in depression. This modern model views elevated MAO-A levels as a pathologic process that results in excessive loss of 3 major monoamines, since increasing monoamine levels through antidepressant inhibition of MAO-A or inhibition of monoamine transporter function are long-standing therapeutic treatments. 30 This model also predicts that indices of monoamine loss should be best detected in subgroups with high severity of particular symptoms. Therefore, investigations that compare monoamine abnormalities between depressed and healthy individuals and do not selectively sample individuals with severe symptom clusters should find abnormalities in depression at a rate exceeding chance but not at a frequency near 100%, as is observed. 4-8,30,38

In this advanced monoamine model, it is proposed that long-term rather than short-term monoamine loss is important for several reasons. First, the period for which monoamine receptor abnormalities are found in the studies directly supporting this model 9,8,36,38 spans the months to years an MDE is typically present before treatment. 1 Second, long-term increasing of monoamine levels reduces symptoms substantially more than short-term increasing of monoamine levels. 30 Third, monoamine levels increased in the long term, consequent to antidepressant administration, influence secondary and tertiary messenger system targets, such as cyclic adenosine monophosphate response element binding protein and brain-derived neurotrophic factor, particularly in animal models. 45 Available evidence demonstrates that these targets are abnormal during MDEs. 43 An advanced model of long-term monoamine loss has the advantage of potentially being consistent with secondary and tertiary messenger theories of depression if long-term monoamine loss influences the same secondary and tertiary messenger targets as monoamine levels increased in the long term.

An important facet of this advanced monoamine model is that, depending on the combinations of long-term serotonin, norepinephrine, or dopamine loss, one would expect different combinations of the associated symptoms during depressive episodes. This is entirely consistent with the particular definition of an MDE that requires 5 of 9 symptoms. 43 In addition, this advanced monoamine model proposes that variable levels of long-term monoamine loss result in variable levels of symptom severity across individuals, as is commonly observed.

A significant problem in depression research is a lack of valid animal models. 43 An important implication of this study is that new animal models of major depression can be created that have chronic monoaminergic abnormalities similar to what is found in untreated depressive episodes. For example, dexamethasone administration to older Sprague-Dawley rats can increase MAO-A density in the brain by 300%, 45 and Wistar rats can be genetically selected to breed high platelet serotonin transporter density and low platelet serotonin density sublines. 46 Breeding of rat sublines with high brain monoamine transporter density and exposing these animals to an MAO-A–increasing paradigm could generate a new animal model of depression with long-term monoamine loss.

There are some limitations in this work. Our study has the major advantage of measuring MAO-A DVs, in vivo. On the other hand, there are some disadvantages with PET. The resolution of PET does not permit detailed localization of MAO-A at the cellular level. For example, an increase in MAO-A density could be attributed to a greater density of MAO-A per mitochondrion or an increase in mitochondrial density within MAO-A–containing neurons. A second issue is that, although MAO-A DVs is an index of MAO-A density, it also reflects 2 other parameters, namely free and nonspecific binding and MAO-A affinity for the radioligand. These other parameters are unlikely to influence the interpretations of this study. The estimates of free and nonspecific binding in the present study (found by obtaining the difference between total distribution volume 20 and specific distribution volume) were similar in patients and healthy controls, and an elevation in MAO-A affinity would be expected to have a similar functional effect of increasing monoamine removal through increased binding to monoamines. We also acknowledge in the interpretation of this study that there are other neurochemical and
neuropathologic models of depression (which may be interrelated). In addition, this article is not intended to argue that other neurochemical and neuropathologic processes do not play a role in antidepressant treatment. Finally, we acknowledge that scientific models of disease are typically replaced with more complicated scientific models of disease, and it is possible that this new theory of monoamine dysregulation in untreated MDEs will be replaced by a more complicated theory at a future date.

Future study should investigate why MAO-A levels are elevated during MDEs. It is well known that the plasma cortisol concentration is elevated during depression, and it was demonstrated that dexamethasone administration can substantially increase MAO-A activity in 19-month-old Sprague-Dawley rats. Since dexamethasone and cortisol both have agonist effects on glucocorticoid receptors, it is possible (should this animal model be representative of adult humans) that greater cortisol agonist effects during depressive episodes contribute to an elevation in MAO-A levels. It would also be interesting to explore a relationship between genotypes and MAO-A levels through complex models such as gene-environment interaction designs in large samples. It seems unlikely that a simple, single genotype to MAO-A alleles, it can be argued that monoamine transporter and monoamine receptors in medication-free depressed individuals, major depression. Important implications of the new theory of monoamine loss during untreated major depression. This finding has major implications for modernizing the monoamine theory of depression. Taken in conjunction with other studies of serotonin and dopamine receptors in medication-free depressed individuals, it can be argued that monoamine transporter density has a secondary role to influence long-term loss of specific monoamines, resulting in a model of variable severity of long-term monoamine loss during untreated major depression. Important implications of the new monoamine theory of depression are that different combinations of severe long-term monoamine loss can explain the variety of symptom cluster presentations found in MDEs and that great potential exists to generate more complex animal models of persistent monoamine loss that may closely resemble the monoaminergic abnormalities of untreated depression.

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REFERENCES


