Association between the Catechol-O-Methyltransferase (COMT) Val<sup>158</sup>Met Polymorphism and Alexithymia in Patients with Obsessive-Compulsive Disorder

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**Purpose:** Alexithymia, defined as a deficit in the ability to recognize and describe one’s own feelings, may be related to the development and maintenance of obsessive-compulsive symptoms. The aim of this study was to evaluate the association between the catechol-O-methyltransferase (COMT) Val<sup>158</sup>Met polymorphism and alexithymia in patients with obsessive-compulsive disorder (OCD).

**Materials and Methods:** We recruited 244 patients with OCD (169 males, 75 females). Alexithymia was assessed using the 20-item Toronto Alexithymia Scale (TAS-20), and genotyping of the COMT Val<sup>158</sup>Met polymorphism was evaluated.

**Results:** Patients with the COMT Val/Val genotype had significantly higher total and “difficulty identifying feelings” (DIF) subdimension scores than those with the Val/Met or Met/Met genotypes. Patients with the COMT Val/Val genotype had significantly higher “difficulty describing feelings” (DDF) subdimension scores than those with the COMT Val/Met genotype. However, there were no differences in the scores for the “externally oriented thinking” (EOT) subdimension among the three genotypes.

**Conclusion:** These results indicate that the high-activity Val allele of the COMT Val<sup>158</sup>Met polymorphism is associated with increased alexithymic traits in patients with OCD. The present finding suggests that alexithymia is an endophenotype of OCD that is mediated by the COMT Val<sup>158</sup>Met polymorphism.

**Key Words:** Alexithymia, COMT Val<sup>158</sup>Met polymorphism, endophenotype, obsessive-compulsive disorder, Toronto alexithymia scale

**INTRODUCTION**

Alexithymia is characterized by difficulties in identifying and describing one’s own feelings. As highly alexithymic individuals are poorly equipped psychologically, alexithymia seems to be an independent risk factor for various medical and psychiatric conditions such as hyperthyroidism, somatoform disorder, depression, eating disorders, and substance dependence.

With regard to obsessive-compulsive disorder (OCD), there have been several studies of alexithymia. Kang, et al. reported that 41% of patients in an OCD group scored in the alexithymic range in contrast to only 4% of subjects in a healthy control group. OCD patients with poor insight were more alexithymic than those with good insight. In OCD, alexithymic traits were associated with age at onset, anxiety level, and sexual or religious obsessions. In a recent study, OCD patients with higher alexithymic traits were also found to have a dysregulated cholesterol imbalance, which in turn may be associated with suicidal regulation.

Alexithymia can best be viewed within the framework of dys-
functional emotion regulation and recognition. Although the cause of alexithymia remains unclear, there are several lines of evidence suggesting the involvement of genetic influences. A family study showed that alexithymic characteristics demonstrated significant intrafamilial associations in a normal population. Large-scale twin studies showed that genetic factors could account for 30–42% of the individual variations of alexithymia. One recent study consisting of 1444 twin pairs reported that individual variations of alexithymia were shaped by both genetic and environmental factors. In addition, although still very limited, a small number of studies have suggested that specific genetic variants of several candidate genes, including those encoding the serotonin transporter, brain-derived neurotrophic factor (BDNF), and dopamine receptor D2 (DRD2), may exert influence on alexithymic traits. Despite the existing controversies, many neuroimaging studies suggest that various brain areas, particularly those involved in emotional processing including the limbic area [anterior cingulate cortex (ACC), anterior insula, and amygdala] and prefrontal cortex (medial and orbitofrontal cortices), might be associated with alexithymia. These brain circuits are subject to dopamine (DA) neurotransmission, which reportedly modulates cognitive and emotional processes. Considering that catechol-O-methyltransferase (COMT) is a major metabolizing enzyme of DA that is mainly located in prefrontal and temporal cortical structures, the COMT gene is an attractive candidate gene for alexithymia. A common polymorphism in the COMT gene is Val^158^Met (rs4680), where methionine (Met) is substituted for valine (Val). The Val variant has enzymatic activity that is 3–4 times higher than the activity in Met carriers. Therefore, Met carriers have higher cortical concentrations of DA, and a number of imaging studies have reported that the COMT Val^158^Met polymorphism can influence emotional processing.

The aim of this study was to investigate the influence of the COMT Val^158^Met genotype on alexithymia, particularly in patients with OCD. Many of the previous genetic studies on alexithymia recruited participants only from the normal population, thus limiting such studies due to the narrow variability in the alexithymic scores, which in turn reduced their power to detect differences. Therefore, using samples with a larger variability in alexithymia would be more advantageous. Currently, only a small number of studies have been reported regarding the association between alexithymia and the COMT Val^158^Met polymorphism in healthy populations or in patients with various mental disorders, and none of these studies involved OCD patients. Hence, we investigated the relationship between COMT Val^158^Met polymorphism and alexithymic traits in patients with OCD, which presumably show more variability in alexithymia. In addition, because alexithymia is heritable, it might be a candidate endophenotype for OCD. Therefore, elucidating the influence of the COMT on alexithymic traits may be helpful in identifying predisposing genes for OCD.

**MATERIALS AND METHODS**

**Participants**
We recruited 244 Korean patients (169 males, 75 females, mean age 30.27±10.76 years) from the OCD clinic at Severance Hospital, Yonsei University Health System, which is a tertiary referral hospital in Korea. The primary diagnoses of OCD and other comorbid psychiatric conditions in patients were determined based on the patient version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, assessed by a trained psychiatrist (S. J. Kim). Exclusion criteria for OCD patients demanded the absence of significant medical or neurologic illness and any other Axis I disorders except for comorbid major depressive disorder (MDD). All patients were in different stages of OCD with differing degrees of severity, and all patients were taking psychotropic medications (mainly selective serotonin reuptake inhibitors and/or low-dose benzodiazepines). All participants gave written informed consent prior to beginning the study. The study protocol was approved by the Institutional Review Board of Severance Hospital.

**Measures**

**Assessment of alexithymia**
The degree of each patient’s alexithymia was measured using the 20-item Toronto Alexithymia Scale (TAS-20), a self-report questionnaire that utilized a five-point Likert-type scale. The TAS-20 comprised three subdimensions: 1) difficulty identifying feelings (DIF) seven items, 2) difficulty describing feelings (DDF) five items, and 3) externally oriented thinking (EOT) eight items. All participants completed the Korean version of the TAS-20.

**Measures of clinical symptoms**
The severities of the patients’ OCD symptoms were evaluated using the Yale-Brown obsessive compulsive scale (Y-BOCS). Levels of depressive symptoms were assessed using the Montgomery-Åsper Depression Rating Scale (MADRS).

**Genotyping**
Peripheral blood samples were obtained from each subject, and genomic DNA was extracted from the leukocytes. Genotyping of the COMT Val^158^Met polymorphism was performed via a single-base primer extension assay using the ABI PRISM SNaPShot Multiplex kit (ABI, Foster City, CA, USA). The forward and reverse primer pairs used for the SNaPshot assay were 5’-ATCAACCCCGACTGTGCC-3’ (forward) and 5’-CTTTTCAGGTCCTGACAACG-3’ (reverse).

**Statistical analyses**
A Pearson correlation analysis was conducted to examine the relationships among TAS-20 total and subdimension scores, Y-
BOCS, MADRS, and age. Multivariate analyses of covariance (MANCOVAs) were computed using the total score and three subdimension scores of the TAS-20 as the dependent variables and the genotypes (Val/Val, Val/Met, and Met/Met) as fixed factors, with the potential confounding factors (Y-BOCS, MADRS, and age) as the covariates to detect the genetic influence of the COMT Val<sup>158</sup>Met polymorphism. Post-hoc analyses were performed using the Bonferroni method. Significance levels were set at <i>p</i> < 0.05. All tests were two-tailed. All statistical analyses were performed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

### RESULTS

The demographic and clinical characteristics of the patients in this study are presented in Table 1. The frequency of the COMT Val<sup>158</sup>Met polymorphism was 53.7% (n=131) for the Val/Val genotype, 38.5% (n=94) for the Val/Met genotype, and 7.8% (n=19) for the Met/Met genotype. This distribution was similar to previous Korean reports and was in accordance with the Hardy-Weinberg equilibrium (χ<sup>2</sup>=0.139; <i>p</i>=0.710). There were no differences in the total and subdimension scores of the TAS-20 between male and female OCD patients (F=1.265; df=3, 172; <i>p</i>=0.288; data not presented). The total and DIF scores of the TAS-20 were correlated with Y-BOCS (all <i>p</i>&lt;0.01), MADRS (all <i>p</i>&lt;0.01), and age (B&lt;0.05 and <i>p</i>&lt;0.01, respectively). The DDF score was correlated with age (<i>p</i>&lt;0.01); however, the EOT score was not correlated with those variables (Table 2). Therefore, we included Y-BOCS, MADRS, and age as covariates in subsequent analyses.

A three-way MANCOVA revealed a main effect of the COMT Val<sup>158</sup>Met polymorphism on the total and subdimension scores of the TAS-20 (F=2.132; df=6, 334; <i>p</i>=0.049) (Table 5). The subjects with the COMT Val/Val genotype had significantly higher total TAS-20 scores than those with the Val/Met genotype (p=0.018) and also tended to have higher total TAS-20 scores than those with the Met/Met genotype (p=0.062). The subjects with the COMT Val/Val genotype had significantly higher DIF subdimension scores than those with the Val/Met or Met/Met genotypes (p&lt;0.05 for all comparisons). Subjects with the COMT Val/Val genotype had significantly higher DDF subdimension scores than those with the COMT Val/Met genotype (p=0.037). However, there was no statistically significant association between the different COMT Val<sup>158</sup>Met genotypes and the patients’ EOT scores.

### Table 1. Demographic and Clinical Characteristics of the Sample (n=244)

| Variable          | Mean (SD)/n (%) |
|-------------------|-----------------|
| Sex               |                 |
| Male              | 169 (69.30)     |
| Age (yrs)         | 30.27 (10.76)   |
| Onset age (yrs)   | 18.76 (9.21)    |
| Education (yrs)   | 13.02 (3.07)    |
| Y-BOCS total score| 21.81 (6.46)    |
| MADRS total score | 16.01 (7.29)    |
| TAS-20 score      |                 |
| Total             | 55.54 (10.99)   |
| DIF               | 19.48 (6.64)    |
| DDF               | 15.39 (4.36)    |
| EOT               | 20.67 (3.91)    |
| Comorbidity       |                 |
| Depression        | 68 (27.87)      |
| Other anxiety disorders | 34 (13.93) |
| Other psychiatric conditions | 6 (2.46) |
| COMT genotype     |                 |
| Val/Val           | 131 (53.70)     |
| Val/Met           | 94 (38.50)      |
| Met/Met           | 19 (7.80)       |
| Medications       |                 |
| SSRIs             | 244 (100)       |
| Escitalopram      | 131 (53.69)     |
| Fluoxetine        | 70 (28.69)      |
| Sertraline        | 31 (12.70)      |
| Paroxetine or fluvoxamine | 12 (4.92) |
| Antipsychotics    | 35 (14.34)      |
| Risperidone       | 19 (7.79)       |
| Aripiprazole      | 15 (6.15)       |
| Olanzapine        | 1 (0.41)        |

SD, standard deviation; Y-BOCS, Yale-Brown obsessive-compulsive scale; MADRS, Montgomery-Asperg Depression Rating Scale; TAS-20, Toronto Alexithymia Scale-20; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; COMT, catechol-O-methyltransferase; SSRI, selective serotonin reuptake inhibitor.
Table 2. Correlation among TAS-20 Total and Subdimension Scores, Y-BOCS, MADRS, Age, and Sex

|                  | DIF     | EOT     | TAS-20 total | Y-BOCS | MADRS | Age   |
|------------------|---------|---------|--------------|--------|-------|-------|
| DIF              | 0.631†  | -0.047  | 0.838†       | 0.179† | 0.343†| -0.201†|
| DDF              | 0.238†  | 0.963†  | 0.063        | 0.322  | 0.019 | 0.091 |
| EOT              | 0.423†  | 0.093   | 0.019        | 0.979  | 0.026 |       |
| TAS-20 total     | 0.167†  | 0.342†  | -0.154*      | 0.91   |       |       |
| Y-BOCS           | 0.336†  | 0.021   | -0.043       | -0.047 |       |       |
| MADRS            | -0.043  |         |              |        |       |       |

TAS-20, Toronto Alexithymia Scale-20; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; Y-BOCS, Yale-Brown obsessive-compulsive scale; MADRS, Montgomery-Åsperg Depression Rating Scale.

Table 3. TAS-20 Total and Subdimension Scores According to COMT Val/Met Genotype

| MANCOVA                  | Genotype               | a. Val/Val (n=131) | b. Val/Met (n=94) | c. Met/Met (n=19) | F    | p value | Post-hoc (p value) |
|--------------------------|------------------------|--------------------|--------------------|--------------------|------|---------|-------------------|
|                          | Hotelling’s trace F=2.305, df (6, 468), p=0.033 |                    |                    |                    |      |         |                   |
| DIF                      | Val/Val                | 20.79±6.61         | 18.22±6.60         | 16.74±5.04         | 5.736| 0.004   | a>b (0.031), a>c (0.021) |
|                          | Val/Met                | 16.21±4.32         | 14.56±4.42         | 13.84±3.20         | 4.444| 0.013   | a>b (0.037)        |
|                          | Met/Met                | 20.89±4.07         | 20.34±3.77         | 20.79±3.63         | 0.575| 0.564   |                   |
| Total                    | Val/Val                | 57.88±11.18        | 53.13±10.40        | 51.37±8.88         | 6.346| 0.002   | a>b (0.009), a>c (0.032) |

TAS-20, Toronto Alexithymia Scale-20; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; MANCOVA, multivariate analysis of covariance (covariates: Y-BOCS, MADRS, age); Y-BOCS, Yale-Brown obsessive-compulsive scale; MADRS, Montgomery-Åsperg Depression Rating Scale; COMT, catechol-O-methyltransferase.

Table 4. Demographic Data, Y-BOCS, MADRS, TAS-20, and COMT Val/Val-Met Genotype Distribution between OCD without MDD and OCD with MDD

|                  | OCD without MDD (n=176) | OCD with MDD (n=68) | v/χ² | p value                          |
|------------------|-------------------------|---------------------|------|----------------------------------|
| Age (yrs)        | 30.28±10.98             | 30.24±10.25         | 0.026| 0.979                            |
| Sex              | Male 118 (67.0%)         | Male 51 (75.0%)     | 1.458| 0.227                            |
|                  | Female 58 (33.0%)        | Female 17 (25.0%)   |      |                                  |
| Y-BOCS score     | 20.80±6.18              | 24.43±6.45          | -4.064| <0.001                          |
| MADRS score      | 12.43±4.66              | 25.26±3.96          | -20.070| <0.001                          |
| TAS-20 score     | 53.28±10.59             | 61.40±9.84          | -5.475| <0.001                          |
|                  | 18.17±5.34              | 22.88±6.21          | -5.232| <0.001                          |
|                  | 14.51±4.11              | 17.66±4.19          | -5.339| <0.001                          |
|                  | 20.60±3.93              | 20.85±3.90          | -0.447| 0.656                            |
| COMT genotype    | Val/Val88 (50.0%)        | Val/Met84 (63.2%)   | 3.469| 0.176                            |
|                  | Val/Met73 (41.5%)        | Val/Met21 (30.9%)   |      |                                  |
|                  | Met/Met15 (8.5%)         | Met/Met4 (5.9%)     |      |                                  |

SD, standard deviation; Y-BOCS, Yale-Brown obsessive-compulsive scale; MADRS, Montgomery-Åsperg Depression Rating Scale; TAS-20, Toronto Alexithymia Scale-20; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; COMT, catechol-O-methyltransferase; OCD, obsessive-compulsive disorder; MDD, major depressive disorder.

Table 5. TAS-20 Total and Subdimension Scores According to COMT Val/Val-Met Genotype in OCD Subjects without Comorbid Major Depressive Disorders

| MANCOVA                  | Genotype               | a. Val/Val (n=88) | b. Val/Met (n=73) | c. Met/Met (n=15) | F    | p value | Post-hoc (p value) |
|--------------------------|------------------------|--------------------|--------------------|--------------------|------|---------|-------------------|
|                          | Hotelling’s trace F=2.132, df (6, 334), p=0.049 |                    |                    |                    |      |         |                   |
| DIF                      | Val/Val                | 19.72±6.58         | 16.85±5.97         | 15.53±4.27         | 5.953| 0.003   | a>b (0.013), a>c (0.034) |
|                          | Val/Met                | 15.38±4.21         | 13.73±3.96         | 13.27±3.37         | 3.988| 0.021   | a>b (0.037)        |
|                          | Met/Met                | 20.67±4.20         | 20.52±3.60         | 20.53±4.03         | 0.049| 0.952   |                   |
| Total                    | Val/Val                | 55.76±11.66        | 51.09±9.31         | 49.33±8.55         | 5.296| 0.006   | a>b (0.018), a>c (0.062) |

TAS-20, Toronto Alexithymia Scale-20; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; MANCOVA, multivariate analysis of covariance (covariates: Y-BOCS, MADRS, age); Y-BOCS, Yale-Brown obsessive-compulsive scale; MADRS, Montgomery-Åsperg Depression Rating Scale; COMT, catechol-O-methyltransferase; OCD, obsessive-compulsive disorder.

Post-hoc (Bonferroni method). Results are presented as mean±SD.
DISCUSSION

The present study investigated the influence of the COMT Val^{158}Met polymorphism on alexithymia in patients with OCD. We found that patients with the Val/Val genotype had significantly higher alexithymia than those with the Val/Met or Met/Met genotypes. These results remained significant after excluding patients with comorbid MDD.

To date, only a small number of studies on the association between alexithymia and the COMT gene exist. Similar to our study, Ham, et al.\textsuperscript{22} found that healthy Korean subjects with the Val/Val genotype of the COMT Val^{158}Met polymorphism had significantly higher TAS-20 total scores than those with the Val/Met or Met/Met genotypes. Although the differences between genotypes for each of the subdimension scores (DIF, DDF, and EOT) did not reach statistical significance, subjects with the Val/Val genotype seemed to have higher DIF, DDF, and EOT scores with an effect size of 0.2–0.8, suggesting that the reason statistical differences were not found might have been due to the limited sample size and variance. Hermes, et al.\textsuperscript{23} also investigated the association between the COMT Val^{158}Met polymorphism and alexithymia in 120 healthy students and 120 patients with mental disorders. Unlike our study, the authors of this previous study did not find any differences in the total or subdimension scores on the TAS-20 between the different COMT Val^{158}Met genotypes in either group. However, this previous study and our study had several significant differences. First, the genotype distributions of the COMT Val^{158}Met polymorphism between the two studies were different (Val/Val: 53.7%, Val/Met: 38.5%, and Met/Met: 7.8% in our sample vs. Val/Val: 21.6%, Val/Met: 52.1%, and Met/Met: 26.3% in their sample). Second, our sample consisted of only patients with OCD, whereas their study was performed in healthy controls and in patients with heterogeneous psychiatric conditions. Third, the ethnic, cultural, and geographical backgrounds of the participants differed between the two studies. Although the exact reasons for the discrepancies between the results of this previous study and those of our own are unclear, the above-mentioned factors likely played a significant role.

As COMT is a critical determinant of prefrontal DA flux, our results showing higher alexithymia in patients with the Val/Val genotype (higher COMT activity) suggest that lower DA levels in the prefrontal cortex are linked to more alexithymic traits. Walter, et al.\textsuperscript{13} reported the influence of two DA-relevant genetic polymorphisms [BDNF and DRD2 ankyrin repeat and kinase domain containing 1 (ANNK1)] on alexithymia. In their study, BDNF 66Met+/DRD2 ANNK1 A1+-carriers had the highest TAS-20 total scores, as well as the highest DIF subdimension scores. They suggested that the less-activated dopaminergic pathway in the BDNF 66Met+/DRD2 ANNK1 A1+-carriers might lead to reduced activation of the ACC via the mesocortical dopaminergic pathway, which in turn may lead to impaired monitoring functions and deficient conscious emotional awareness. Additionally, in Parkinson’s disease, reduced nigrostriatal and prefrontal DA transmission produces alexithymic characteristics such as numbness in affect, reduced motivation, and difficulties recognizing emotional expressions.\textsuperscript{31} Furthermore, depleted DA in the ACC or orbitofrontal cortex may underline both the cognitive and emotional manifestations of alexithymia in Parkinson’s disease.\textsuperscript{31}

Contrary to the significant associations identified between genotypes and DIF and DDF scores, we did not find any association between EOT scores and the COMT Val^{158}Met polymorphism. In our study, compared to patients with the Val/Met or Met/Met genotypes, patients with the Val/Val genotype of the COMT Val^{158}Met polymorphism had greater difficulty in identifying their feelings and differentiating between feelings and bodily sensations (DIF). We also found that patients with the Val/Val genotype had more difficulty describing their feelings (DDF) yet had externally oriented feelings (EOT) that were highly similar to those of patients with the Val/Met or Met/Met genotype. Although there is some debate over this issue, items from the DIF and DDF subdimensions of the TAS-20 may constitute a single factor, with items from the EOT subdimension being loaded on a different factor.\textsuperscript{32} Unlike DIF or DDF, EOT does not seem to be associated with psychopathology. In contrast to DIF or DDF, there was no association between EOT and negative affect.\textsuperscript{33} EOT differs from DIF and DDF in that it is not an emotional deficit, but is instead a thinking style that de-emphasizes emotion.\textsuperscript{34} Henry, et al.\textsuperscript{35} insisted that EOT may be separate from the alexithymic construct as it reflects a style of avoiding introspective thought rather than specifically measuring alexithymia. Another possible reason for the lack of association between COMT genotypes and EOT might be related to the poor psychometric properties of the EOT subdimension. In fact, this subdimension often showed low internal consistency, possibly due to response style effects, as it has four negatively keyed items.\textsuperscript{36} For any variable, poor measurement reliability reduces the possibility of detecting an association with another variable.

It has been hypothesized that both cognitive and emotional processing depend on DA modulation, though at different points on the inverted-U function that relates DA tuning to performance. Accordingly, if cognitive processing is optimized, emotional processing may become inefficient and vice versa. In fact, a number of studies have reported that the Met allele of the COMT Val^{158}Met polymorphism, which results in higher DA levels in the prefrontal cortex, is associated with better cognitive processing yet worse emotional processing.\textsuperscript{37} Therefore, the results of our study demonstrating higher DIF and DDF scores in patients with the Val/Val genotype suggest that these two subdimensions of the TAS-20 rely on cognitive processes rather than on emotional processes. Several recent studies have indicated that there are cognitive and affective dimensions of alexi-
thymia and that each dimension might have different underlying neural correlates. Moreover, the TAS-20 is known to assess the cognitive component, which refers to the processing of emotions at the cognitive level and comprises a limited ability to identify, verbalize, and analyze one's feelings; as such, it is not a good representation of the emotional component.

The present study had several limitations. First, the TAS-20 used in this study was a self-report questionnaire and was not an observer-based interview. Although the TAS-20 is widely used and shows positive correlations with clinician rating scales of alexithymia, future studies that combine this self-report questionnaire with an observer-based alexithymia interview should be conducted. Second, all of the patients were taking various selective serotonin reuptake inhibitors (SSRIs), and certain patients were also taking second-generation antipsychotics when they were enrolled, which may have had confounding effects on our results. To rule out these potential confounding effects, further research involving drug-naïve or drug-free OCD patients is warranted.

Finally, we only investigated one well-known single nucleotide polymorphism of the COMT gene. However, due to the complex features of alexithymia, many genetic variants and/or interactions between multiple genes may underlie this trait.

In conclusion, a genetic variant of the COMT gene may influence alexithymic traits in patients with OCD. The Val/Val genotype of the COMT Val<sup>108</sup>/Met polymorphism might predict several alexithymic traits such as DIF and DDF. To confirm the influence that the COMT gene has on alexithymic traits, further investigations using both self-report and clinician-administered rating scales for alexithymia in a large number of subjects with other psychiatric illnesses and normal populations are warranted.

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