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The genetic association between personality and major depression or bipolar disorder. A polygenic score analysis using genome-wide association data

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The relationship between major depressive disorder (MDD) and bipolar disorder (BD) remains controversial. Previous research has reported differences and similarities in risk factors for MDD and BD, such as predisposing personality traits. For example, high neuroticism is related to both disorders, whereas openness to experience is specific for BD. This study examined the genetic association between personality and MDD and BD by applying polygenic scores for neuroticism, extraversion, openness to experience, agreeableness and conscientiousness to both disorders. Polygenic scores reflect the weighted sum of multiple single-nucleotide polymorphism alleles associated with the trait for an individual and were based on a meta-analysis of genome-wide association studies for personality traits including 13,835 subjects. Polygenic scores were tested for MDD in the combined Genetic Association Information Network (GAIN-MDD) and MDD2000 + samples (N = 8921) and for BD in the combined Systematic Treatment Enhancement Program for Bipolar Disorder and Wellcome Trust Case–Control Consortium samples (N = 6329) using logistic regression analyses. At the phenotypic level, personality dimensions were associated with MDD and BD. Polygenic neuroticism scores were significantly positively associated with MDD, whereas polygenic extraversion scores were significantly positively associated with BD. The explained variance of MDD and BD, ~0.1%, was highly comparable to the variance explained by the polygenic personality scores in the corresponding personality traits themselves (between 0.1 and 0.4%). This indicates that the proportions of variance explained in mood disorders are at the upper limit of what could have been expected. This study suggests shared genetic risk factors for neuroticism and MDD on the one hand and for extraversion and BD on the other.

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Introduction

The relationship between major depressive disorder (MDD) and bipolar disorder (BD) remains controversial. Both are characterized by depressive episodes, whereas BD is, in addition, characterized by manic episodes. Research into risk factors for MDD and BD reports similarities and differences.

This also applies to studies investigating the association between personality and MDD or BD. Most of these studies have focused on the personality traits neuroticism/negative emotionality (N), extraversion/positive emotionality (E) and, to a lesser extent, agreeableness (A), conscientiousness (C) and openness to experience (O). N is commonly defined as a tendency toward emotional instability. E is characterized by a disposition toward positive emotions, gregariousness and the tendency to be active, seek out stimulation and enjoy the company of others. O involves active imagination, aesthetic attentiveness, variety preference and intellectual curiosity. A can be defined as the tendency to be cooperative and compassionate rather than suspicious and antagonistic toward others. Finally, the dimension C reflects traits of self-discipline, carefulness, thoroughness, organization, deliberation and achievement.

In a recent meta-analysis on the relationship between personality and MDD, MDD was significantly associated with higher N and with lower C with a Cohen’s d of 1.33 for N and −0.90 for C. The association with C became weaker (Cohen’s d −0.59) after controlling for N, but remained significant. Although a negative link between E and MDD has often been reported, the effect was modest and not significant in the meta-analysis (Cohen’s d −0.62). The associations with O and A were not significant either.

Studies on the association between personality and BD are sparser, but have consistently shown higher levels on N and O and lower levels of C compared with normal controls. This suggests that subjects with MDD and BD are similar regarding N and C and differ regarding O. This is supported by studies directly comparing personality profiles for MDD and BD. All studies showed the same trend with higher O in BD subjects than in MDD subjects. This was significant in only one of these studies, but the other samples included far fewer subjects and probably did not have the power to detect the effect (<100 BD subjects versus ~1000 subjects) Most of these studies have been performed in MDD or BD subjects in an euthymic phase; thus, the results do not reflect a state effect of mood on personality.

Mood disorders and personality traits are partly influenced by genetic risk factors. Heritability estimates are ~40% for MDD, 50% for personality traits and between 60 and 90% for BD. This raises the question whether associations between personality and mood disorders are explained by shared genetic risk factors. So far, this has only been investigated for MDD. Twin studies have provided considerable support for overlapping genetic risk factors influencing N and MDD (reviewed in Middeldorp et al.). Fewer twin studies have investigated the association with other personality traits and MDD suggesting a smaller, but significant genetic correlation between C and O and MDD, but not between E and MDD.

Genome-wide association (GWA) data also provide an opportunity to investigate whether traits are influenced by overlapping genetic risk factors. On the basis of GWA results for one trait, for instance, neuroticism, performed in one sample (the discovery sample), a polygenic score is calculated for each individual in another sample (the target sample). These polygenic scores are obtained by taking a set of top single-nucleotide polymorphisms (SNPs), for example, all SNPs with P-values below 0.1 and multiplying the individual’s genotypic score (0, 1 or 2) by the effect of the SNP. If the polygenic scores are significantly related to a second trait, for instance, MDD, in the target sample, this indicates that the two traits, namely neuroticism and MDD, are influenced by overlapping genetic risk factors. In this manner, a genetic relationship was observed for schizophrenia and BD and for MDD and anxiety. In the former study, polygenic scores based on a GWA study in schizophrenia explained between 1 and 2% in BD. In the latter study, polygenic scores based on a MDD GWA study explained ~2% of the variance in anxiety disorders.

This study investigates the genetic association between the five personality traits N, E, O, A and C and MDD, as well as BD. On the basis of the results of a GWA meta-analysis of N, E, O, A and C in >13,000 subjects, individual polygenic scores were calculated and tested for their effect on case–control status in 2 combined target MDD samples and in 2 combined target BD samples totaling 8921 and 6329 subjects, respectively. We first asked whether the genetic association between N and MDD as found in the twin studies is confirmed using polygenic score analysis and to what extent the other personality traits are genetically associated with MDD. Second, we investigated the genetic relationship between personality and BD. Finally, we asked what the differences are between the genetically mediated personality profiles underlying BD and MDD.

Materials and methods

Subjects, measurement instruments and genotyping

Discovery samples for personality. The GWA meta-analyses were performed on personality data collected from nine samples: SardiNIA–Italy, Erasmus Rucphen Family study (ERF)–The Netherlands, Study of Addiction: Genetics and Environment (SAGE)–United States of America, Helsinki Birth Cohort Study (HBCS)–Finland, Nicotin Addiction Genetics Study/Interactive Research Project Grants (NAG/IRPG) study–Australia, Queensland Institute of Medical Research (QIMR) adolescent study–Australia, Lothian Birth Cohort 36 (LBC36)–United Kingdom, Baltimore Longitudinal Study of Aging (BLSA)–United States of America and Estonian Genome Project of University of Tartu (EGPUT)–Estonia. For a detailed description of these samples, we refer to de Moor et al. The total number of subjects available for the meta-analyses was 13,835. Sample sizes ranged from 600 to 3972 individuals. Mean age ranged from 19 to 70 years. In 5 studies, the mean age was between 40 and 50 years, in 1 study the mean age was 19 years, and in 3 studies, the mean age was between 60 and 70 years. It must be noted that the meta-analysis as described in de Moor et al. also included the GAIN-MDD sample. This sample was excluded in the personality traits meta-analyses for this...
study as the GAIN-MDD set served as one of the target samples (see below for the description of the sample).

Personality scores were assessed with NEO Personality Inventory–Revised (NEO-PI-R), NEO-PI-3 or the NEO Five-Factor Inventory. In each study, scores for the 5 factors (N, E, O, A and C) were based on the item responses of the NEO-Five-Factor Inventory (12 items per phenotype). Summed scores were computed for all five personality dimensions.

DNA was extracted from blood samples. Genotyping was performed on Illumina platforms (Illumina, San Diego, CA, USA) in all studies, except in SardiNIA in which an Affymetrix platform (Affymetrix, Santa Clara, CA, USA) was used. Genotype data were checked in each study independently, using slightly different inclusion criteria. Among the basic checks that were performed are checks for European ancestry, Mendelian errors, gender inconsistencies and high genome-wide homozygosity. Genotype data were further cleaned based on Hardy–Weinberg equilibrium, minor allele frequencies, SNP call rate (% of subjects with missing genotypes per SNP) and sample call rate (% of missing SNPs per subject). Imputation to genotypes per SNP was carried out using IMPUTE for SAGE B (Mountain View, CA, USA) using a set of four proprietary, high-density oligonucleotide arrays. Imputation was carried out using IMPUTE software with HapMap phase II CEU data as the reference sample (NCBI build 36/UCSC hg18, Bethesda, MD, USA). Imputation was carried out using IMPUTE for SAGE and EGPUT samples. For the other samples, genotype data were imputed using MACH software.

**Target samples for MDD and BD.** Polygenic scores were tested in two MDD case–control samples: GAIN-MDD and MDD2000þ and in two BD case–control samples: Wellcome Trust Case–Control Consortium (WTCCC) and Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). The four samples have been described in detail elsewhere. MDD and BD diagnoses were assessed with commonly used standardized interviews.

**GAIN-MDD.** This sample consisted of subjects from two large-scale longitudinal studies, the NESDA (Netherlands Study of Depression and Anxiety) and the NTR (Netherlands Twin Register). The mean ages of cases (N=1738) and controls (N=1802) were 43 and 45 years, respectively. Inclusion criteria for MDD cases were a lifetime diagnosis of MDD-related traits. In addition, controls and their parents were required to have been born in the Netherlands or Western Europe. Only one control per family was selected.

Individual genotyping was conducted by Perlegen Sciences (Mountain View, CA, USA) using a set of four proprietary, high-density oligonucleotide arrays. Imputation was carried out using IMPUTE software with the HapMap phase II CEU data as the reference sample using NCBI build 36 (UCSC hg18).

**MDD2000+.** The second MDD target sample consisted of 2101 cases and 3280 screened controls, a subset of the MDD2000+ sample after excluding samples that overlapped with the discovery and GAIN-MDD samples. Samples were provided by the Queensland Institute of Medical Research (QIMR, Brisbane, QLD, Australia), NESDA, NTR, the University of Edinburgh (UoE, Scotland, UK) and the MGS (Molecular Genetics of Schizophrenia) study (controls only, United States). Control subjects from NTR who also participated in the GAIN-MDD study (N=223) were excluded, as well as cases and controls from the NAG/IPRG study that had been included in the personality traits meta-analysis (N=500). Mean ages of cases and controls were 41 and 48 years, respectively. MGS controls completed an online questionnaire including the short-form CIDI, supplemented by questions about schizophrenia, psychosis and BD. Controls were required to never have met the criteria for these disorders or MDD.

Genotyping was conducted on different Illumina and Affymetrix platforms. Imputation was conducted in four analysis sets (I317, I370, I610 and A6.0) to a common set of SNPs present in HapMap3 CEU/TSI, using Beagle 3.04,51,52

**Wellcome Trust Case–Control Consortium.** The sample comprises 1868 BD cases. They were over the age of 16 years and of European descent. Individuals who had been in contact with mental health services were recruited if they suffered from a major mood disorder in which clinically significant episodes of elevated mood had occurred, such as bipolar I disorder (71% cases), schizoaffective disorder bipolar type (15% cases), bipolar II disorder (9% cases) and manic disorder (5% cases).

Half of the 3000 controls came from the 1958 British Birth cohort (58C) and were between 44 and 45 years of age at the time of DNA collection. The other half was selected from blood donors. Age ranged from 18 to 69 years. Analyses were carried out on observed genotypes. Ancestry principal components were available for 3919 subjects (1452 cases and 2467 controls), and these subjects were included in the current analyses.

**Systematic Treatment Enhancement Program for Bipolar Disorder.** STEP-BD was a US national, longitudinal public health initiative designed to examine the effectiveness of treatments and their impact on the course of BD. Over a 7-year period, 4361 participants were enrolled across 20 sites and followed for up to 2 years. From the parent STEP-BD study, 2089 individuals were enrolled in a genetic substudy. Mean age was 43 years. Only non-Hispanic Caucasian individuals with European ancestry based on self-reported race and ethnicity information were included.

Controls were used from the NIMH (National Institute of Mental Health) Genetics Repository and were MGS controls. This study included 1507 cases with bipolar I and bipolar II disorder and 903 controls.

Genotyping was performed using the Affymetrix GeneChip Human Mapping 500K Array Set. Beagle, version 3.1.1 was used to impute missing genotypes, with HapMap2 (Centre d’Etude du Polymorphisme Humain from Utah population, release 23, forward strand) as the reference panel.

**Statistical analyses**

**GWA meta-analyses of personality.** Genome-wide association meta-analyses were carried out as described in de
Moor et al.\textsuperscript{25} without inclusion of the GAIN-MDD data. Meta-analyses were based on GWA analyses for the five personality traits conducted in each study with linear regression (under an additive model) and included sex and age as covariates. Meta-analyses of the results were conducted by the weighted inverse variance method as implemented in METAL (http://www.sph.umich.edu/csg/abecasis/metal/index.html),\textsuperscript{53} which computes a pooled effect estimate ($\hat{\beta}$), its s.e. and its $P$-value by weighing the effect estimates of individual samples by the inverse of its variance and by taking into account the direction of effect.

**Polygenic score analyses.** The genetic associations of the five personality scales with MDD and BD were analyzed for each personality scale separately in the combined samples for MDD and in the combined samples for BD. Polygenic scores were calculated and tested for their effect according to Purcell et al.\textsuperscript{23} Five sets of SNPs were selected from the GWA results for each of the five NEO personality scales meta-analyses. This selection of SNPs was based on their nominal $P$-value ($P_{\text{discovery}}$) for association with the NEO-personality scale in the discovery sample. For each of the five personality scales, five sets of SNPs were selected, one with $P_{\text{discovery}}$ threshold 0.1, one with threshold 0.2, one with threshold 0.3, one with threshold 0.4 and one with threshold 0.5. These sets of SNPs were used to calculate the polygenic scores for subjects in the four target samples by multiplying the dosage score of risk allele count per SNP from 0 to 2 by the beta, summed over all SNPs in the considered set of SNPs and divided by the total number of SNPs.\textsuperscript{23} In short: $\sum$dosageScore*beta/N(SNPs). Dosage scores were used to account for the uncertainty in the imputed genotypes. We calculated individual scores for each set of SNPs using the PLINK software.\textsuperscript{54}

The association of the polygenic scores with MDD was evaluated by logistic regression. Ancestry principal components were included as covariates. The explained variance was based on Nagelkerke's $R^2$. To analyze polygenic scores in the combined samples (GAIN-MDD + MDD2000 + and WTCCC + STEP-BD), polygenic scores were corrected for ancestry principal components. Next, a logistic regression with sample as covariate was performed with standardized residuals of polygenic scores as independent variables.

**Results**

To illustrate the association between personality dimensions and MDD or BD, Table 1 shows the scores for five personality traits measured with the NEO Five-Factor Inventory\textsuperscript{2} in GAIN-MDD controls, GAIN-MDD cases and STEP-BD cases at entry to the study. Four of the five personality scales were significantly different in MDD patients compared with controls: N scores were higher, whereas A, E and C scores were lower in depressed subjects (all $P$-values < 0.0001 in a t-test). As described in Barnett et al.,\textsuperscript{6} BD patients at a euthymic phase significantly differed from the population norms for all scales exhibiting higher levels of N and O and lower levels of E, C and A.

The sets of SNPs with $P$-values below 0.1, 0.2, 0.3, 0.4 and 0.5 based on the results in the discovery sample included the number of SNPs as expected for these $P$-values, that is, ~ 200 k, 400 k, 600 k, 800 k and 1 million SNPs, respectively. The overlap with SNPs used to calculate polygenic scores in the target samples was 100% for the GAIN-MDD sample, 40% for the MDD2000 + sample, 20% for the WTCCC sample and 90% for the STEP-BD sample. The lower overlap is due to the use of HapMap 3 as a reference set in the MDD2000 + sample and to the use of observed genotypes only in the WTCCC sample.

Figure 1 presents the results of the logistic regression analysis for MDD with the personality polygenic scores based on the GWA meta-analysis as independent variables. Significant positive associations were found between MDD and polygenic N scores for all sets of SNPs. In addition, significant negative associations were found between MDD and polygenic E scores based on the sets of SNPs with $P$-values < 0.1 and < 0.5 and polygenic C scores based on the sets of SNPs with $P$-values < 0.3 to < 0.5. These effects explained 0.1% of the variance in MDD ($P$-value < 0.05).

Figure 2 shows results of the logistic regression analysis for BD. Polygenic E scores were significantly positively related to BD, explaining 0.1% of the variance ($P$-value < 0.05).

The analyses were also carried out in the four samples separately to check for heterogeneity in the results across studies. None of the polygenic personality scores were significantly associated with MDD in the MDD2000 + study with the proportion of explained variance always below 0.1%. This is in contrast to the analyses of the GAIN-MDD sample in which polygenic N scores based were significantly higher in MDD cases than in controls, explaining between 0.2 and 0.4% of the variance ($P$-values < 0.005) (see Supplementary Figure 1a). Moreover, polygenic C scores, based on the sets of SNPs with $P$-values < 0.3 and < 0.5, were lower in MDD cases explaining 0.2 and 0.3% of the variance ($P$-values

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**Table 1** Mean (s.d.) neuroticism (N), extraversion (E), agreeableness (A), openness to experience (O) and conscientiousness scores (C) in GAIN-MDD controls and GAIN-MDD cases and STEP-BD cases

<table>
<thead>
<tr>
<th></th>
<th>Controls MDD</th>
<th>MDD</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14.6 (5.9)</td>
<td>27.3 (8.1)*</td>
<td>30.9 (8.6)**</td>
</tr>
<tr>
<td>E</td>
<td>30.5 (6.7)</td>
<td>23.1 (7.0)*</td>
<td>23.2 (7.5)**</td>
</tr>
<tr>
<td>A</td>
<td>33.4 (4.7)</td>
<td>31.4 (5.4)*</td>
<td>29.9 (6.9)**</td>
</tr>
<tr>
<td>O</td>
<td>25.0 (5.7)</td>
<td>24.8 (5.6)</td>
<td>29.5 (7.0)**</td>
</tr>
<tr>
<td>C</td>
<td>33.5 (4.8)</td>
<td>25.6 (6.1)*</td>
<td>28.8 (8.0)**</td>
</tr>
</tbody>
</table>

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.

* $P<0.00001$ compared with GAIN-MDD controls.

** $P<0.001$ compared with population norms.\textsuperscript{6}

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**Figure 1** Explained variance by the five personality traits polygenic scores in MDD in GAIN-MDD + MDD2000 +, \(1^*P<0.05\). MDD, major depressive disorder.
<0.05). Thus, the significant results for MDD are mostly driven by the GAIN-MDD study.

The picture looks different for BD (see Supplementary Figures 1b and 1c). In the STEP-BD sample, polygenic E scores based on the sets of SNPs with P-values < 0.4 and 0.5 and polygenic C scores based on the sets of SNPs with P-values < 0.1 showed a significant positive and negative association, respectively, with BD. There were no significant effects detected in WTCCC, but the proportion of explained variance by polygenic E scores is similar as in the STEP-BD study. This suggests that, although separate studies are sometimes underpowered to detect the small effects of polygenic E scores, they both contribute to the significant effects as found in the analyses of the combined samples.

Given the relatively low proportion of variance explained by the polygenic personality scores for mood disorders, additional regression analyses were performed to detect the proportion of variance explained by the polygenic personality scores in the personality trait scores themselves. It was tested whether the polygenic N, E, O, A and C scores, as used in the analyses above, significantly predicted the respective N, E, O, A and C trait scores as measured in GAIN-MDD subjects. The polygenic scores explained between 0.1 and 0.4% of the corresponding personality trait scores (P-values between 0.0003 and 0.2) with the best results for polygenic O scores predicting O and the worst results for polygenic A scores predicting A.

Discussion

This study suggests that MDD is influenced by similar genetic risk factors as neuroticism (N) and that BD is influenced by similar genetic risk factors as extraversion (E). Both associations are positive: that is, genetic risk factors related to a higher N score increase the risk for MDD and genetic risk factors related to a higher E score increase the risk for BD. Moreover, genetic risk factors influencing conscientiousness (C) and E might be negatively associated with MDD, but results are less consistent.

The results for MDD agree with earlier genetic epidemiological research. Several studies have already suggested an overlap in genetic risk factors for neuroticism and MDD as reviewed by Middeldorp et al.17 A negative genetic correlation between MDD and C has also been reported.18

The genetic relationship between personality and BD has not been investigated before. With the exception of E, the absence of a genetic association between personality traits and BD is surprising given the phenotypic relationships between BD and the five personality traits found in the STEP-BD sample (Table 1) and other studies.5–9 Furthermore, the genetic association with E was positive, whereas the phenotypic association found in the total sample of STEP-BD subjects was negative. However, Barnett et al.6 showed in the same study sample that high N was related to a depression-prone BD course, whereas high E was related to a manic-prone BD course. Similar findings were reported by Quilty et al.55

The explained variance in MDD and BD by the polygenic scores was very modest. However, this was also true for prediction of the personality traits themselves with comparable proportions of explained variance (up to 0.4%) and P-values. Thus, the proportions of explained variance for mood disorders are at the upper limit of what could have been expected. Still, these numbers are lower than the explained variance of ~2% reported for polygenic schizophrenia scores predicting BD and polygenic MDD scores predicting anxiety disorders.23,24 This can be partly explained by a lack of power. Although the discovery sample was large with >13 000 subjects, only a few SNPs reached genome-wide significance and the deviation of the line of observed P-values from the line of expected P-values in the QQ plots is also modest.25 As the individual effect sizes of SNPs are small, the error of the estimates is relatively large. Therefore, the explained variance in a prediction analysis is low.56 This is comparable to the results of the analyses of GWA data for intelligence, which showed that the proportion of variance explained by all SNPs varied between 40 and 51%, whereas prediction analyses only explained 1% of the variance in intelligence.57

An additional explanation could be the large age differences in the studies included in the discovery set, resulting in top hits in the meta-analysis that reflect genetic variants associated with stability in personality traits from adolescence through older age. It is possible that genetic risk factors influencing stability over time are less related to MDD and BD than genetic risk factors for personality that are mostly important around early adulthood, the period of onset of MDD and BD. However, longitudinal twin studies suggest that genetic influences on personality are for the largest part stable, thus without much change in genetic risk factors across time (see, for example, Kandler et al.58 for a study in adults and Gillespie et al.59 and Hopwood et al.60 for studies in adolescents and young adults). A strength of our study, on the other hand, is that polygenic scores were determined from GWA study results in a sample of individuals without mood disorders and are not confounded by mood state in the cases.

The STEP-BD sample and the MDD2000 + sample both included MGS controls. That is no problem as the discovery sample and target samples were not overlapping.

Analyses of the effects of the polygenic personality scores on mood disorders in the four separate studies indicated that for BD, results were consistent over studies, whereas for MDD, results were mainly driven by the GAIN-MDD study. There does not seem to be an obvious explanation for the absence of effect in the MDD2000 + sample. The overlap in
SNPs used to calculate polygenic scores was far lower in the MDD2000+ sample than in the GAIN-MDD sample because of the use of different reference sets for the imputation, HapMap3 in MDD2000+ and HapMap2 in MDD-GAIN. HapMap3 includes less SNPs but is based on more subjects. However, the overlap in SNPs was also lower in the WTCCC sample, whereas their results were similar to the results in the STEP-BD sample, which had a high overlap in SNPs. Therefore, the low overlap in SNPs does not seem to explain the difference in results between the MDD2000+ and the MDD-GAIN sample. Given the repeatedly found genetic correlation between N and MDD, it seems most likely that the finding in MDD2000+ is a false negative finding.

Despite the low explained variance, the results of this study indicate some interesting issues regarding the etiology of MDD and especially BD. Although studies investigating the phenotypic association between personality and MDD, as well as BD suggest that both disorders are related to high N and that, in addition, BD is related to high O, the genetic association shows a different picture of shared genetic risk factors for N and MDD on the one hand and for E and BD on the other. As previous studies have already pointed to differences in personality profiles between depression-prone and manic-prone BD patients, these results imply that BD is a heterogeneous disorder with different expressions related to different, genetically influenced, personality profiles. This view is supported by the finding that an association with polymorphisms in the GABA receptor γ1 subunit gene is most significant in cases fulfilling the Research Diagnostic Criteria for schizo-affective disorder. 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