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ARTICLE

A three-factor model of common early onset psychiatric disorders: temperament, adversity, and dopamine

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Commonly comorbid early onset psychiatric disorders might reflect the varying expression of overlapping risk factors. The mediating processes remain poorly understood, but three factors show some promise: adolescent externalizing traits, early life adversity, and midbrain dopamine autoreceptors. To investigate whether these features acquire greater predictive power when combined, a longitudinal study was conducted in youth who have been followed since birth. Cohort members were invited to participate based on externalizing scores between 11 to 16 years of age. At age 18 (age 18.5 ± 0.6 y.o.), 52 entry criteria meeting volunteers had a 90-min positron emission tomography scan with [^{18}F]fallypride, completed the Childhood Trauma Questionnaire, and were assessed with the Structured Clinical Interview for DSM-5. The three-factor model identified those with a lifetime history of DSM-5 disorders with an overall accuracy of 90.4% ($p = 2.4 \times 10^{-5}$) and explained 91.5% of the area under the receiver operating characteristic curve [95% CI: .824, 1.000]. Targeting externalizing disorders specifically did not yield a more powerful model than targeting all disorders ($p = 0.54$). The model remained significant when including data from participants who developed their first disorders during a three-year follow-up period ($p = 3.5 \times 10^{-5}$). Together, these results raise the possibility that a combination of temperamental traits, childhood adversity, and poorly regulated dopamine transmission increases risk for diverse, commonly comorbid, early onset psychiatric problems, predicting this susceptibility prospectively.

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INTRODUCTION

Converging epidemiological [1–5] and molecular genetic evidence [6–8] raises the possibility that many psychiatric disorders reflect the varying expression of overlapping developmental trajectories [4, 9]. One of the largest trajectories is characterized by diverse externalizing (EXT) behaviors [5, 10–12], including poor impulse control, dysregulated affect, and altered responses to rewards and punishments [13, 14].

EXT traits are likely mediated by multiple neurobiological systems [15, 16]. One implicated system has shown associations between low midbrain dopamine autoreceptor levels [17, 18], increased dopamine release [19, 20], and various EXT-related features, including impulsivity, sensitivity to punishment and novelty seeking [20, 21]. In laboratory animals too, low midbrain autoreceptors and elevated dopamine transmission can increase the salience of both positive and negative stimuli [22–30], promote novelty seeking and motor impulsivity [16, 28–31], and reduce the ability to disambiguate optimal choices [32–34]. Stressful events can aggravate these features, including the fomenting of dopaminergic [35, 36] and behavioral hyperreactivity [35, 37] and susceptibility to mental health problems [38, 39].

Prompted by the above findings, we tested, in young adults who have been followed since birth, whether the combination of all three factors (EXT, childhood trauma, dopamine regulation) predicts clinical outcomes. It was hypothesized that higher EXT traits, greater early life adversity, and lower midbrain dopamine autoreceptor availability would predict the presence of early onset commonly comorbid psychiatric conditions.

METHODS

Participants

All participants were born between 1996 and 1998, lived in the Montreal or Quebec City area in Canada, and had been followed since birth [40–42]. Fifty-eight volunteers (36 F/22 M) underwent magnetic resonance imaging (MRI) and [^{18}F]fallypride positron emission tomography (PET) scans. Six were excluded from the current analyses: two due to not having Childhood Trauma Questionnaire (CTQ) data and four due to BP_{ND} values being

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Table 1. Participant characteristics (means ± standard deviations).

N	52
Female/Male	30/22
Age (years)	18.5 ± 0.58
Ethnicity	N = 50 White European
Education (number of years)	11.92 ± 1.05
Externalizing trait score	1.40 ± 1.05
Age of alcohol use onset	14.77 ± 1.86
Lifetime occasions of binge drinking	28.52 ± 45.20
Lifetime occasions of alcohol use (including intoxication and non-intoxication)	88.29 ± 101.81
Lifetime occasions of cannabis use	149.15 ± 406.89, range: 0 to 2011
Age of onset of cannabis use	15.68 ± 1.45
Lifetime occasions of drug use, excluding cannabis	13.65 ± 64.33, range: 0 to 426
Current tobacco smoking status*	46No/5Yes

*missing data from one participant

outliers (±3 SD) (Table 1 and Supplementary Table 1). The final sample consisted of 52 participants (30 F/22 M), mean age at the time of scanning was 18.5 (SD = 0.6 years). Forty-one participants (22 F/19 M) had one or more follow-up interview (age at last assessment: 21.0 ± 0.9 years). Ethics approval was obtained from McGill University and Sainte-Justine University Hospital Research Ethics Boards, and all participants provided written informed consent. Further details are in Jaworska et al. [21].

Externalizing (EXT) scores

Externalizing trait scores were measured annually between ages 10 and 16 through self-report (Quebec Longitudinal Study of Child Development; QLSCD, $n = 53$) or teacher ratings (Quebec Newborn Twin Study; QNTS, $n = 5$) using the Social Behavior Questionnaire (SBQ) [43, 44]. Mean scores were calculated for the following SBQ subscales: hyperactivity, impulsivity, oppositional behavior, non-aggressive behavioral problems, physical aggression, proactive aggression, indirect aggression and reactive aggression. Composite EXT trait scores were aggregated using a minimum of two years' data between 10 and 16 years [5, 40]. Mean EXT scores during these years correlated with those obtained earlier in life (1–5 and 6–10 years) [40]. For the current study, cohort members were invited to participate if they scored in either the top or bottom 30% of EXT trait scores, as established in the first wave of QLSCD cohort members ($n = 242$, born in 1996) [40].

Assessments

At their index assessment prior to the PET and MRI scans, all participants were interviewed face-to-face with the Structured Clinical Interview for DSM-5 (SCID) [45] and administered the CTQ [46]. Follow-up telephone assessments were then conducted annually for the next three years. The CTQ measures early life adversity, including emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect [46]. It has been validated in French [47] and has good psychometric properties [48]. Elevated CTQ scores are associated with poor cognitive function across multiple domains [49] and diverse psychiatric disorders [50, 51].

Magnetic resonance imaging (MRI)

MRI scans were acquired on each participant for anatomical co-registration using a 3 T Siemens Trio TIM scanner (McConnell Brain Imaging Center, Montreal Neurological Institute) with a Magnetization Prepared Rapid Acquisition sequence (slice: 1 mm, TR: 2300 ms, TE: 3.42 ms, flip angle: 9°, FOV: 256 mm, Matrix: 256 × 256). MRI and PET data were coregistered to aid anatomical precision when defining the regions of interest (ROIs).

PET imaging

Dopamine D2 receptor levels were measured using the high affinity dopamine D2/D3 receptor ligand, [^{18}F]fallypride, and a 90-minute PET scan on a high-resolution research tomograph (HRRT). Following cannula insertion into the left antecubital vein for tracer administration, a 6-min ^{137}Cs transmission scan was obtained for attenuation correction. The [^{18}F]fallypride tracer (prepared as previously described [19]) was administered as a 1-min intravenous bolus, with emission scans acquired concurrently in list mode over 90 minutes (participants were instructed to remain awake). The mean ± SD injected [^{18}F]fallypride dose was 123.39 ± 7.59 MBq, injected mass was 1.46 ± 3.90 nmol, and molar activity at time of injection was 381.08 ± 819.99 GBq/μmol. There were no statistically significant differences in injected dose, mass or molar activity between participants with and without psychiatric diagnoses (p values > 0.4; Supplementary Table 2).

PET images were reconstructed using the Ordinary Poisson Ordered Subset Expectation Maximization (OP-OSEM) reconstruction algorithm (10 iterations, 16 subsets). This included correction for non-uniformities, attenuation, scattered and random coincidences, and motion. To reduce partial volume effects, resolution modeling using the point spread function was implemented in image reconstruction. Motion correction was based on a data-driven motion estimation and correction method that estimates rigid-body motion between dynamic frames. Further details are in Jaworska et al. 2020 [21].

MRI and PET analyses

The imaging data set was obtained from previously analyzed images [21]. Binding potential non-displacement (BP_{ND}) values were derived from the primary region of interest (ROI), the midbrain dopamine cell body region, consisting of the ventral tegmental area and substantia nigra, and seven exploratory regions of interest (ROIs) further implicated in the regulation of mood and motivational states and impulsive behaviors (superior frontal gyrus, medial frontal gyrus, medial orbito-frontal gyrus, middle frontal gyrus, insula, amygdala, and hippocampus) [21]. ROI masks were defined using standard masks on the MNI152 template which were coregistered to each individual's MRI scan using linear and nonlinear transformations [52]. These ROI masks were then applied to each summed PET image using nonlinear co-registration. Time-activity curves were extracted from each ROI in native PET space using tools developed by the Turku PET Center (http://www.turkupetcentre.net/). BP_{ND} values (i.e., equilibrium ratio of specifically bound to non-displaceable radioligand in tissue) were derived from ROIs using the simplified reference tissue model [53] with cerebellar gray matter as the reference region.

Statistical analyses

Binomial logistic regression analyses were conducted to test whether midbrain [^{18}F]fallypride BP_{ND} values, EXT and CTQ scores, converted to Z scores, predicted the presence of lifetime DSM-5 diagnoses. All analyses were run for diagnoses obtained at the time of or prior to the PET scan and again including diagnoses obtained during the follow-up interviews.

Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure [54]. A Bonferroni correction was applied using all seven terms (midbrain BP_{ND}, EXT, CTQ, midbrain*ln_midbrain, EXT*ln_EXT, CTQ*ln_CTQ, and constant) in the overall model resulting in statistical significance being defined as $p < 0.0071$ [55]. Based on this assessment, all continuous independent variables were linearly related to the logit of the dependent variable.

Receiver operating characteristic (ROC) curves were created for each model, and the area under the curve (AUC) was used to evaluate the overall model's strength. ROC curves illustrate the ability of a binary classifier to discriminate groups as the threshold is varied. The graph is created by plotting the true positive rate or sensitivity on the y axis, and the false positive rate or (1—specificity) on the x axis. The area under the ROC curve measures how well the model can identify positive and negative cases. The AUC ranges between 0 and 1. The closer the AUC is to 1, the better the model. An AUC close to 1 is able to correctly identify patients with and without diagnoses, an AUC close to 0 identifies group designation incorrectly, and an AUC close to 0.5 indicates that the model has no classification ability [56].

All hypotheses were tested using two-tailed statistics. Unless otherwise noted, all analyses were performed using IBM SPSS version 26 with the following add-ons: Complex Sampling & Testing, Forecasting & Decision Trees, and Custom Tables & Advanced Statistics.

RESULTS

Lifetime psychiatric diagnoses

At their index interview, 23% of participants met criteria for one or more lifetime DSM-5 disorders. By their last interview, this had

Table 2. Comparison of overall model strength at each step of sequential binomial logistic regression.

	EXT	EXT + CTQ	EXT + CTQ + Midbrain BP_{ND}
Chi Squared	$\chi^2(1) = 18.359$ $p = 0.000018$	$\chi^2(2) = 19.435$ $p = 0.000060$	$\chi^2(3) = 24.109$ $p = 0.000024$
Nagelkerke R^2	0.450	0.472	0.562
Classification predictive accuracy	87% (45/52)	87% (45/52)	90% (47/52)
ROC AUC (95% CI)	0.855 (0.713 – 0.998)	0.872 (0.749 – 0.995)	0.915 (0.824 – 1.000)
Sensitivity	50% (6/12)	58% (7/12)	75% (9/12)
Specificity	98% (39/40)	95% (38/40)	95% (38/40)
Positive predictive value	86% (6/7)	78% (7/9)	82% (9/11)
Negative predictive value	87% (39/45)	88% (38/43)	93% (38/41)

ROC AUC = receiver operating characteristic area under the curve.

Table 3. Role of each standardized predictor variable in binomial logistic regression, at index interview.

	EXT score Score range 0 to 3.98	Midbrain BP_{ND} Score range 1.26 to 2.80	CTQ total Score range 25 to 61
Beta ± Standard Error	2.258 ± 0.72	−1.129 ± 0.58	0.800 ± 0.43
Wald	9.880	3.833	3.484
p	0.002	0.050	0.062
Odds ratio (95% CI)	9.567 (2.340–39.115)	3.096 (0.999–9.615)	2.225 (0.961–5.151)

increased to 31%. The specific diagnoses included substance use disorders (SUDs), unipolar mood disorders, attention deficit-hyperactivity disorder (ADHD), panic disorder, generalized anxiety disorder, adjustment disorders, dyslexia, binge eating disorder, and conduct disorder (Supplementary Tables 3A and 3B).

Three-factor model predicts lifetime psychiatric disorders at index interview

The three-factor model was statistically significant ($p = 2.4 \times 10^{-5}$), correctly classifying 90% of cases and explaining 56% (Nagelkerke R^2) of the variance in DSM-5 diagnoses. Sensitivity was 75%, specificity was 95%, positive predictive value was 82%, negative predictive value was 93%, and ROC AUC was 92% [95% CI: .824, 1.000], considered an outstanding level of discrimination (Table 2) [57].

All three factors contributed to the model. Adding CTQ total scores as the third factor strengthened the model (compared to EXT + midbrain BP_{ND}, $p = 0.05$). Adding midbrain [^{18}F]fallypride BP_{ND} values as the third factor strengthened the model (compared to EXT + CTQ, $p = 0.03$). Adding EXT scores as the third factor strengthened the model (compared to CTQ + midbrain BP_{ND}, $p = 5.0 \times 10^{-6}$). In comparison, the model was not improved by the addition of BP_{ND} values from the seven exploratory ROIs ($p \geq 0.37$).

Within the three-factor model, standardized EXT scores (Wald = 9.880, $p = 0.002$) and midbrain [^{18}F]fallypride BP_{ND} values (Wald = 3.833, $p = 0.05$) were statistically significant after controlling for the influence of the two other factors. One standard deviation (SD) increases in CTQ and EXT scores were associated with two- and 10-times greater odds of having a lifetime DSM diagnosis, respectively. A one SD decrease in midbrain [^{18}F]fallypride BP_{ND} values was associated with three times higher odds (Table 3).

Three-factor model predicts lifetime EXT disorders at index interview

The three-factor model predicted lifetime EXT disorders alone at index interview. The model was primarily driven by EXT traits ($p = 0.008$). When adding midbrain BP_{ND} values and CTQ scores, the former strengthened the model (compared to EXT + CTQ, $p = 0.027$) while the latter did not (compared to EXT + midbrain BP_{ND}, $p = 0.225$). More importantly, this three-factor model for EXT disorders was not stronger than the one capturing all expressed DSM-5 disorders (AUC ROC curves for EXT vs. all disorders, $t(102) = 0.6191$, $p = 0.54$) [58], plausibly reflecting the propensity of people with EXT disorders to develop internalizing disorders and vice versa [59] (Table 4).

Three-factor model predicts lifetime psychiatric disorders at follow-up

At the last follow-up interview, the logistic regression model was statistically significant ($p = 3.5 \times 10^{-5}$), explained 51% (Nagelkerke R^2) of the variance in DSM-5 diagnoses, and correctly classified 81% of cases. Sensitivity was 63%, specificity was 89%, positive predictive value was 71% and negative predictive value was 84%. Of the three predictor variables only EXT trait score was statistically significant (Wald = 11.948, $p = 0.001$), but inclusion of CTQ scores and midbrain BP_{ND} values yielded what is considered an excellent level of discrimination [57] (EXT alone, AUC ROC = 0.855 [95% CI: .713, 0.998]; EXT + CTQ + midbrain BP_{ND}, AUC ROC = 0.898 [95% CI: 0.795, 1.000]).

Three-factor model is accurate in men and women

Male participants were more likely to have diagnoses of ADHD and SUDs while female participants more frequently met criteria for mood and anxiety disorders (Supplementary Table 4). Overall, lifetime psychopathology was observed in similar proportions of males and females (6/22 vs. 10/30; no significant difference, Fisher's exact test, $p = 0.76$). At the index interview, the model remained significant with the addition of sex as a fourth factor ($p = 3.4 \times 10^{-5}$). Sex itself was not a significant predictor of a lifetime DSM-5 diagnosis (Wald = 0.374, $p = 0.54$), nor was the four-factor model (EXT + CTQ + midbrain BP_{ND} + sex) significantly different from the three-factor model ($p = 0.54$) (Table 5). When additional diagnoses from the follow-up interviews were included, the model with sex as a fourth variable remained significant ($p = 7.4 \times 10^{-5}$). Again, however, sex itself was not a significant predictor of lifetime DSM-5 diagnosis (Wald = 0.843, $p = 0.36$) and the four-factor model (EXT + CTQ + midbrain BP_{ND} + sex) was not significantly different from the three-factor model ($p = 0.35$).

Table 4. Role of each standardized variable in predicting EXT disorders at index interview.

	EXT score	Midbrain BP_{ND}	CTQ total
Beta ± S.E.	2.679 ± 1.017	−1.411 ± 0.738	0.674 ± 0.550
Wald	6.945	3.654	1.500
p	0.008	0.056	0.221

Table 5. Comparison of model strength in predicting EXT disorders with vs. without sex as a factor. In the general population, EXT disorders exhibit a sex difference in incidence rates. Proportions similar to this population distribution were seen in the present study but adding sex as a fourth factor did not significantly strengthen the model targeting these EXT disorders ($p = 0.061$) or the model targeting all DSM-5 disorders ($p = 0.54$).

	Midbrain BP_{ND} + EXT + CTQ	Midbrain BP_{ND} + EXT + CTQ + sex
Chi squared	$\chi^2(3) = 18.552$ $p = 0.000338$	$\chi^2(4) = 22.055$ $p = 0.000195$
Nagelkerke R^2	0.549	0.633
Classification predictive accuracy	90% (47/52)	90% (47/52)
ROC AUC (95% CI)	0.949 (0.890 – 1.000)	0.956 (0.902 – 1.000)
Sensitivity	43% (3/7)	57% (4/7)
Specificity	98% (44/45)	96% (43/45)
Positive predictive value	75% (3/4)	67% (4/6)
Negative predictive value	92% (44/48)	93% (43/46)

DISCUSSION

Our study's primary objective was to test whether a three-factor model, composed of features with modest transdiagnostic predictive value when tested in isolation, could more powerfully predict the presence of lifetime psychiatric disorders in young adults who have been followed from birth. As hypothesized, the combination of higher EXT traits, greater levels of childhood adversity, and lower levels of midbrain D2 receptors identified, with high accuracy and statistical robustness, participants with any lifetime history of psychiatric illness, both at the index interview and at follow-up.

To our knowledge, this is the first investigation to study all three factors together. In comparison, each individual factor has been found to increase risk for psychopathology. As a start, both epidemiological [1–5] and molecular genetic [6–8] studies suggest that EXT traits reflect a developmental trajectory from which diverse psychiatric disorders can emerge. This includes substance use and cluster B personality disorders, as well as problems commonly considered internalizing disorders [1, 4, 5, 59].

Childhood trauma is arguably the prototypical transdiagnostic risk factor, increasing the probability of both internalizing and EXT disorders in adolescence and adulthood [51, 60]. The replicated associations with early life adversity noted, some people exhibit striking resilience [61, 62]. The factors accounting for these different responses to adversity are thought to include variability in coping skills [63] and pre-existing temperament [64]. The present study raises the possibility that a third contributing factor is midbrain dopamine cell reactivity.

Midbrain D2 receptors are primarily autoreceptors [65]. In humans, somatodendritic autoreceptors are present on dopamine cells that project to the striatum but not cells that project to the cerebral cortex [66–69]. Despite this, there is evidence from studies in laboratory animals that altered mesostriatal dopamine transmission affects functioning within the larger mesocorticolimbic circuitry. In these studies, poorly regulated dopamine cell reactivity can lead to cognitive deficits [32, 70, 71], sub-optimal choices [32, 33], impulsivity [29, 72], and susceptibility to depressive phenotypes [23]. Adverse outcomes might be particularly profound when elevated mesostriatal dopamine transmission is combined with reduced or asynchronous cortical dopamine function [23, 32, 72]. Indeed, across diagnostic categories, there is evidence of poorly regulated dopamine transmission [20, 21, 73–77] with *DRD2* variants constituting a transdiagnostic risk gene [78].

The study's fourth finding was related to sex. As expected, males were more likely than females to be diagnosed with attention deficit and substance use disorders and less likely to meet criteria for mood and anxiety disorders. This noted, both in our study and in the general population, the lifetime prevalence of psychiatric illness overall is similar for men and women and adding sex as a predictor did not improve the model's strength. These observations suggest that the three investigated factors influence susceptibility to psychiatric disorders in both males and females irrespective of how the susceptibility comes to be expressed.

The breadth of diagnoses predicted by the model raises the possibility that it contributes to the hypothesized p factor that has been proposed to affect risk for all common psychiatric disorders [4–6, 79]. The specific processes composing p have been little studied, but some work suggests that they include poor impulse control over emotions and difficulties in reality testing [4]. The findings reported here might identify sources of these alterations.

Strengths and limitations

The present research benefitted from prospectively collected behavioral traits and clinical outcomes. It is also, to our knowledge, the first PET study in a longitudinally followed birth cohort. These strengths noted, the results should be interpreted in light of the following considerations. First, all three factors contributed to the model's strength after controlling for the influence of the two other factors indicating that they are not interchangeable proxies of each other. This noted, only EXT was statistically significant as a standalone variable. This observation suggests that CTQ scores and midbrain D2 receptor availabilities contribute through interactions with the other variables. Although the present sample is reasonably large for a PET study, it is not large enough to interrogate further these potential statistical interactions; we can therefore primarily conclude that high statistical power is provided by the model overall. Second, the three-factor model also predicted the presence of EXT disorders uniquely. In this analysis, the smaller number of affected cases decreased further the ability to disentangle contributions of each individual factor, but the effect appeared to be driven by EXT scores and midbrain [^{18}F]fallypride BP_{ND} values. Additional work will be needed to better capture the model's strength for EXT vs. internalizing

disorders, but longitudinal research indicates that a history of disorders from one cluster predicts higher risk for both "homotypic" and "heterotypic" conditions [59]. Consistent with the proposition that the studied risk factors are not specific to a single cluster, the three-factor model was not significantly better at capturing EXT disorders than all occurring DSM-5 disorders. Third, much of the data was collected prospectively, but definitive statements about causality are not possible. Instead, the study identifies a model that predicts clinical outcomes. Fourth, the sample was relatively homogenous, composed primarily of francophone youth of European descent. Future studies should test whether the model generalizes to other populations. Fifth, the index interviews were conducted face-to-face, but the follow-up interviews were by telephone, potentially diminishing the quality of information from these later assessments. Sixth, participant attrition may not have been random. However, these sub-samples did not differ on key variables, including age, EXT score, or proportion with a lifetime history of DSM-5 disorders (Supplementary Table 5). Finally, the project's PET tracer, [^{18}F]fallypride, binds to both D2 and D3 receptors [80]. Midbrain D2 receptors are primarily located on mesostriatal dopamine neurons where they act to inhibit mesostriatal dopamine release [17, 19, 27]. The majority of midbrain D3 receptors, in comparison, are on terminal regions of descending striatal GABAergic neurons and their activation inhibits cortical dopamine release [18]. Since [^{18}F]fallypride has preferential affinity for D2 [80], our PET data are likely dominated by effects relevant for mesostriatal dopamine transmission. This noted, to the extent that the effect could also include changes to D3 receptors, poorly synchronized striatal and cortical dopamine transmission erodes a wide range of cognito-affective processes [23, 32].

CONCLUSIONS

This first study of the three-factor model supports proposals that many common forms of early onset psychopathology emerge from the varying expression of shared intersecting dimensions [3–5]. Obtaining a better understanding of the identified features could provide targets for early interventions with implications for both nosology and etiology.

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AUTHOR CONTRIBUTIONS

ML conceived of the study and designed it with JS and SMLC. MT, SMLC and NJ collected the data. MI, SMLC, NJ and NCR analyzed the data. MI, SMLC, NJ and ML interpreted the data and wrote the manuscript with input from the other authors (MT, SP, AD, FV, MRB, MB, ROP, SMC, RET, JRS).

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COMPETING INTERESTS

The authors declare no competing interests.

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