



Neuroimaging-Based Deep Learning in Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder

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Deep learning (DL) is a kind of machine learning technique that uses artificial intelligence to identify the characteristics of given data and efficiently analyze large amounts of information to perform tasks such as classification and prediction. In the field of neuroimaging of neurodevelopmental disorders, various biomarkers for diagnosis, classification, prognosis prediction, and treatment response prediction have been examined; however, they have not been efficiently combined to produce meaningful results. DL can be applied to overcome these limitations and produce clinically helpful results. Here, we review studies that combine neurodevelopmental disorder neuroimaging and DL techniques to explore the strengths, limitations, and future directions of this research area.

Key Words: Neuroimaging; Neurodevelopmental disorder; Autism spectrum disorder; Attention-deficit/hyperactivity disorder; Deep learning; Review.

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INTRODUCTION

During the first 12 months of life, various factors such as heredity and environment affect the progression of neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) [1]. Several studies have pointed out that in the case of ASD, behavioral signs may appear during the age of 6–12 months [2], but in clinical settings, on average, clear diagnosis is only possible after 4 years of age [3]. In ADHD, diagnostic accuracy in children older than 7 years of age is limited due to difficulties in distinguishing them from children with normal development [4–7]. Therefore, in longitudinal studies, the stability of ADHD diagnosis before 7 years of age has been a problem; up to 50 other studies have concluded that diagnostic stability rate is below 50% for children under this age [8–11].

To facilitate better course and prognosis of neurodevelopmental disorders, it is important for clinical interventions to precede certain critical periods of brain plasticity development through early and accurate diagnosis. Although early detection of neurodevelopmental disorders is vital, the development of non-invasive, quantitative, and sensitive biomarkers has been insufficient. It would, thus, be valuable to

detect biomarkers (e.g., brain images, blood, genes, pupillometry, etc.) early in development that can differentiate children with neurodevelopmental disorders and those with normal development pathways.

The several potential biomarkers found thus far exist only as sporadic information, and it is difficult to derive meaningful information on diagnosis by collecting them. In order to solve this problem, deep learning (DL) technology can be used to collect biomarker information, allowing early detection of neurodevelopmental disorders in a simple, accurate, timely, and cost-efficient manner.

This review summarizes the latest papers that use DL in the field of neuroimaging in ASD and ADHD research (Table 1). Through our review, the merits and limitations, as well as future directions of neuroimaging-based DL of neurodevelopmental disorders will be brought to light.

DEEP LEARNING

DL involves training and testing a multi-layered neural network using artificial intelligence (AI) to learn complex structures and achieve a high level of abstraction [12]. It is a machine learning technique which is different from existing techniques in that it can acquire optimal representation through consecutive nonlinear transformation of large amounts of raw data. This feature has strengths in terms of abstraction

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and complexity, enabling accurate visual recognition. In the medical field, it has gained a spotlight in the field of radiology, and is used for classification, diagnosis, risk factor analysis, prognosis, and prediction of treatment response. In the field of neuroimaging, it is used for classification and diag-

nosis of neurologic conditions such as stroke, neurodegenerative disorders, and psychiatric disorders [13-18].

DL uses artificial neural networks (ANN), which are modeled on the structure of human neural networks to perform cognitive functions [19]. In a feedforward network, informa-

Table 1. Summary of neuroimaging based deep learning studies

Authors (year)	Sample size	Technique	Features	DL architecture	Comparison	Accuracy (%)
Li et al. (2018) ²³	HC=209 ASD=55	sMRI	WB voxel-level	Multi-channel CNN	HC vs. ASD	76.24
Li et al. (2019) ²⁴	HC=215 ASD=61	sMRI	ROI (amygdala, hippocampus)	Dilated-Dense U-Net	HC vs. ASD	79.9 to 92.3
Yoo et al. (2019) ²⁵	HC=47 ADHD=47	sMRI & DTI & rfMRI	WB voxel-level & region-level	Random forest (RF)	HC vs. ADHD	69.4 & 77.8
Moberget et al. (2019) ²⁶	Cohort=1401*	sMRI & rfMRI	ROI (cerebeilum)	ICA		
Sidhu et al. (2019) ²⁷	HC=124 SPR=55 ADHD=19 ASD=31	rfMRI & tfMRI	WB voxel-level	PCA	HC vs. SPR HC vs. ADHD HC vs. ASD	>80
Xiao et al. (2019) ²⁸	HC=81 ASD=117	rfMRI	WB voxel-level	SAE	HC vs. ASD	96.26
Aghdam et al. (2019) ³⁴	ABIDE I & ABIDE II data [†]	rfMRI	WB voxel-level	CNN	HC vs. ASD	72.73
Deshpande et al. (2015) ³⁵		rfMRI	WB voxel-level	FCC ANN	HC vs. ADHD ADHD inattentive vs. ADHD combined	90 & 95
Jung et al. (2019) ³⁶	HC=125 ASD=86 ADHD=83	rfMRI	WB voxel-level & regional-level	SVM-RFE	HC vs. ASD HC vs. ADHD ASD vs. ADHD	76.3 to 84.1
Kuang et al. (2014) ³⁸	ADHD-200 consortium data	rfMRI	ROI (PFC)	DBN	HC vs. ADHD	44.4 to 80.9
Hao et al. (2015) ³⁹	ADHD-200 consortium data	rfMRI	ROI (PFC, cingulate, somatosensory, visual cortex)	Deep bayesian network	HC vs. ADHD	48.8 to 72.7
Wang et al. (2018) ⁴⁰	ADHD-200 consortium data	rfMRI	WB regional-level	SVM	HC vs. ADHD	78.75
Xu et al. (2020) ⁴²	HC=22 ASD=25	fNIRS	Temporal variation	LSTM, CNN	TD vs. ASD	95
Xu et al. (2019) ⁴³	HC=22 ASD=25	fNIRS	ROI (bilateral inferior frontal gyrus and temporal lobe)	CGRNN	TD vs. ASD	90 to 92.2
Yoo et al. (2019) ²⁵	Training dataset=83 Independent dataset=36	DTI	ROI (10 frontal lobe structures and two major striatal regions)	WEKA	Training dataset vs. Independent dataset	90.0 to 95.5

*philadelphia neurodevelopmental cohort, age 8-23 years, [†]ABIDE I and II: autism brain imaging data exchange I and II. HC: healthy control, ASD: autism sepectrum disorder, ADHD: attention-deficit/hyperactivity disorder, SPR: schizophrenia, MRI: magnetic resonance imaging, sMRI: structural MRI, DTI: diffuse tensor imaging, rfMRI: resting state functional MRI, tfMRI: task-based function MRI, fNIRS: functional near-infrared spectroscopy, WB: whole brain, ROI: region of interest, PFC: prefrontal cortex, ICA: independent component analysis, PCA: principal component analysis, SAE: sparse auto-encoder, CNN: convolutional neural network, FCC ANN: fully connected cascade artificial neural network, SVM-RFE: support vector machine-recursive feature elimination, DBN: deep belief network, SVM: support vector machine, LSTM: long short-term memory, CGRNN: consisting of CNN and GRU, WEKA: waikato environment for knowledge analysis

tion is propagated in one direction from the input to the output layer, whereas in a recurrent network, past information makes feedback links that can affect the output. This connection allows information to be retained in a neural network in a manner similar to memory, and a model capable of processing data can be constructed.

There are two main stages of DL. The first (training) stage acquires the optimal algorithm to perform the desired task (e.g., classification, diagnosis, prediction, etc.) by learning the available data. In the second (test) stage, an evaluation of whether the trained model can accurately distinguish the newly observed data is conducted [20].

Convolutional neural networks (CNN), which are most commonly used in neuroimaging, were developed as models of the visual cortex to process visual information and are a type of feedforward neural network. CNN consists of three layers: input layer, convolutional layer, and pooling layer. The convolutional layer consists of several feature maps. All artificial neurons in a given feature map are connected to the previous layer of the feature map in the same region (local connectivity), and the locality is distinguished by connections with different weights from feature maps in other regions. Therefore, a feature map can be used as a feature detector to scan a pattern type, called a kernel. The process of making local connections with different weights to form numerous kernels is done automatically within the network and without any interventions. When multiple convolutional layers exist, increasing amounts of abstract visual information can be processed [12].

Currently, in addition to CNN, various models such as Fully Convolutional Network and Dilated-Dense U-Net are used in research [12].

NEUROIMAGING-BASED DEEP LEARNING IN PSYCHIATRY

In the field of neuroimaging, the interest in generalization of classification using machine learning is on the rise. DL technology is mainly used in psychiatry as a diagnostic model for distinguishing between patient and normal groups, a model for predicting the risk of developing disorders in a high-risk group, and a model for predicting response to a treatment [12]. A number of studies on diagnostic models have been conducted on Alzheimer's disease and mild cognitive impairment, but the number of studies on neurodevelopmental disorders is small.

In one study, classification using machine learning was performed to evaluate large heterogeneous groups of four diseases: ASD (n=988), ADHD (n=930), post-traumatic stress disorder (n=87), and Alzheimer's disease (n=132) [21]. In this

study, 18 machine learning classifications were applied, and the predictive powers of these classifiers were combined to form one consensus-classifier proposal. The identified functional connection pattern was firmly applied to differences in classification algorithms, age, and data acquisition sites, and was confirmed to have diagnostic predictive ability along with the ability to distinguish statistically significant differences between groups.

Research on neuroimaging-based DL of neurodevelopmental disorders is mainly conducted using magnetic resonance imaging (MRI), functional MRI (fMRI), and functional near-infrared spectroscopy (fNIRS). Most studies focus on evaluating diagnostic accuracy through DL algorithms, and several MRI studies utilize DL to analyze structural differences between brain regions of patient groups and normal development groups to develop biomarkers for early detection.

MAGNETIC RESONANCE IMAGING

In a 2019 study by Moon et al. [22], 40 machine learning algorithm studies for ASD published between 2007 and 2018 were systematically reviewed and meta-analysis was conducted. Among them, meta-analysis of 12 samples using structural MRI revealed that the integrated sensitivity was 0.83, specificity was 0.84, and area under the curve/partial area under the curve (AUC/pAUC) was 0.90/0.83. Based on these results, the authors deemed the accuracy of the machine learning algorithm using structural MRI in ASD diagnosis to be acceptable.

Li et al. [23] applied multi-channel CNN using a patch-level data-expanding strategy to brain MRI data to predict ASD early in life. A total of 264 brain MRI scans [55 ASD groups, 209 normal control (NC) groups] registered in the National Database for Autism Research (NDAR) were collected and areas of brain structures showing statistically significant differences between the ASD and NC groups were selected (data-driven anatomical landmark identification). When the corresponding region was extracted from MRI scans and subjected to DL using a multi-channel CNN, the diagnostic accuracy improved by 24% over a three-dimensional CNN.

Li et al. [24] also used a new DL approach, the Dilated-Dense U-Net, to find ASD neurobiological anomalies and confirm critical timing of the progression through longitudinal studies of amygdala and hippocampus subfield development. They collected 276 longitudinal brain MRI scans (30 ASD, 31 mild autism spectrum, 215 NC groups) registered in the NDAR. Cross-analysis revealed that the ASD group showed bilateral amygdala and bilateral CA1-3 size expansion at 6 months after birth and bilateral amygdala, left CA1-

3, left subiculum size expansion at 24 months after birth. Longitudinal analysis showed that at about 6 months of age, there was a size expansion of bilateral amygdala and bilateral CA1-3 in the ASD group with an increase in the size difference between the groups at around 24 months of age. They suggested that overgrowth of amygdala and CA1-3 starting at 6 months of age may be associated with the expression of ASD, and highlighted the possibility of early ASD detection from 6 months of age onwards.

Yoo et al. [25] confirmed that machine learning using multi-mode neurological imaging and genetic data could distinguish typically developing children from an ADHD group. Polygenetic risk scores calculated from cortical morphology, diffuse scalar and resting state functional connectivity, and norepinephrine/dopamine/glutamate genes were extracted from 47 ADHD children and 47 matched NC children. A model consisting of cortical thickness and volume characteristics achieved a maximum accuracy of 85.1%. Morphological changes across insula, sensory/motor cortex, and ventral frontal cortex were also identified as key predictors, accounting for 18% of the ADHD measurement scale. Dynamic zone homogeneity within the default network accounted for 6.4% of the missing errors in the continuous performance test (CPT) and validity testing achieved an accuracy of 69.4%. The results of this study indicate that structural abnormalities related to salience detection, sensory processing and response suppression can be powerful classifiers for ADHD diagnosis and symptoms.

Evidence is accumulating on the role of the cerebellum in psychiatric diseases such as schizophrenia, bipolar disorder, depression, anxiety disorder, and ADHD; however, little is known about its role during the development of these diseases. Currently, it is unclear whether the morphological aspects of the cerebellum are associated with the expression of specific symptoms. In one study, analysis using machine learning was conducted to determine whether morphological characteristics of the cerebellum could reliably predict general cognitive function and psychiatric symptoms in a large-scale developmental community composed of adolescents [26]. The morphological characteristics of the cerebellum were correlated with both general cognitive function and general psychopathology (mean correlations between predicted and observed values: $r=0.20$ and $r=0.13$, respectively; $p<0.001$). Analysis of specific symptom areas revealed that norm-violating behaviors ($r=0.17$; $p<0.001$), psychotic symptoms ($r=0.12$; $p<0.001$) and anxiety symptoms ($r=0.09$; $p=0.012$) were significantly associated with cerebellar morphology. On the contrary, there were no associations with ADHD, depressive disorder, mania, and obsessive-compulsive disorder symptoms. Cerebellar features appeared to be most important in

predicting general psychopathology, psychotic symptoms, and norm-violating behaviors.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

fMRI measures neural activity using blood oxygenation-level dependent (BOLD) differences. A 2019 meta-analysis study conducted on fMRI and machine learning algorithm studies on ASD published between 2007 and 2018 [22] found the integrated sensitivity to be 0.69, specificity to be 0.66, and AUC/pAUC to be 0.71.

In one study, nonlinear dimensionality reduction (Locally Linear Embedding) was introduced to extract neural activity information using BOLD time-series [27]. The methodology was verified by leave-one-out-cross-validation (LOOCV) accuracy for classification of psychiatric diagnosis using resting state and task-related fMRI. Embedded fMRI showed high diagnostic performance (>80%) for 11 datasets including patients with schizophrenia, ADHD, ASD, and NC. Unlike the original fMRI data, embedded fMRI showed significantly better results than chance classification in ten out of 11 datasets.

Xiao et al. [28] attempted to validate diagnostic classification using DL on the full brain frequency from resting-state fMRI data of 198 school-aged ASD children. The average diagnostic accuracy was found to be 96.26%, sensitivity to be 98.03%, and specificity to be 93.62%. These results show higher diagnostic accuracy of up to 15% when compared with previous studies that classified diagnosis using only one or two frequency bands [29-33].

Aghdam et al. [34] examined whether diagnostic discrimination is possible when resting-state fMRI data of 5–10 year old ASD children is subjected to DL with CNN [34]. Analysis using various methods showed that the maximum diagnostic accuracy was 0.7273, sensitivity was 0.712, and specificity was 0.7348.

In a 2015 study, Deshpande et al. [35] applied a fully connected cascade ANN to compare functional connectivity between ADHD and NC children. Using this method, ADHD children of inattentive and combined subtype and an NC group were classified with an accuracy of 90%, and two subtypes with an accuracy of 95%.

In another fMRI study using machine learning technology, functional connection patterns were examined in ADHD, ASD, and matched typically developing children (7–15 year old males) [36]. In the ASD group, functional connectivity within the limbic system and somatomotor network was increased as compared to the NC group. In addition, it was confirmed that the ADHD group showed an increase in func-

tional connectivity within the limbic system, visual, default mode, somatomotor, dorsal attention, fronto-parietal, and ventral cognitive networks as compared to the ASD group. Using machine learning, ASD and normal groups, ADHD and normal groups, ADHD and ASD groups were classified with accuracies of 76.3%, 84.1%, and 79.3%, respectively.

The ADHD-200 consortium provides open-data sharing of ADHD patients with 776 resting-state fMRI and anatomical datasets aggregated across eight independent imaging sites for better understanding of the neural basis of ADHD. Several studies have been conducted using the ADHD-200 consortium data. Milham et al. used DL to analyze the brain areas that distinguish NC groups from ADHD groups, and found that the prefrontal, cingulate, and visual cortices are the most informative [37]. In a study using the same data, it was found that the prefrontal cortex region could be used to distinguish between the ADHD and NC groups of three different samples with accuracies of 44.4%, 55.6%, and 80.9%, respectively [38]. In a 2015 study, the dataset of prefrontal, cingulate, somatosensory, and visual cortices were combined to distinguish between the ADHD and NC groups of three different samples with accuracies of 48.8%, 54%, and 72.7%, respectively [39]. In a 2018 study by Wang and Jiao [40], data from the ADHD-200 consortium was used to construct a diagnostic model based on support vector machines (SVMs). The performance of the diagnostic model was analyzed using LOOCV and 10-fold cross-validations (CV). LOOCV revealed that the model had 78.75% accuracy, 76% sensitivity, and 80.71% specificity. The 10-fold CV average prediction accuracy was $75.54 \pm 1.34\%$, average sensitivity was $70.5 \pm 2.34\%$, and mean specificity was $77.44 \pm 1.47\%$. The differential pattern of ADHD was investigated using SVM, and the result was consistent with those of the previous studies, highlighting its potential as a biomarker.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

It is known that the ASD patient and normal development groups differ in terms of spontaneous hemodynamic fluctuation in oxygenated hemoglobin (HbO₂) and deoxyhemoglobin (Hb) [41].

According to a study by Xu et al. [42], hemodynamic changes in the temporal cortex of ASD children show weaker stationarity and stronger memory and persistence for wireless shock than typically developing children. When analyzing whether diagnostic differentiation can be accomplished by applying a DL model to the spontaneous hemodynamic fluctuation of the brain over time, the temporal change of HbO₂ showed 91.4% specificity, 98.6% sensitivity, and 95% accuracy.

The temporal change of Hb was able to discriminate between the groups with 94.3% specificity and 97.1% sensitivity.

In a study by Xu et al. [43], fNIRS was used to measure HbO₂, Hb, and total hemoglobin in the bilateral inferior frontal gyrus and bilateral temporal cortex for 480 seconds. The record was divided into 7-second units that were partially overlapped and they examined whether ASD and typically developing children could be differentiated using a convolutional gated recurrent neural network (CGRNN), a multi-layer neural network that combines CNN and gate recurrent unit. As a result, Hb of channel 10 showed 92.2% accuracy, 85% sensitivity, and 99.4% specificity and HbO₂ of channel 43 showed 90.8% accuracy, 87.9% sensitivity, 93.8% specificity. The total hemoglobin of channel 25 was able to discriminate between the ASD and NC groups with 90% accuracy, 81.6% sensitivity, and 98.5% specificity. Xu et al. suggested that the CGRNN model used in the study can be applied clinically in a mere 7 seconds.

MULTIMODAL APPROACHES

In a study that used DL, Yoo et al. [44] sought to determine if pre-treatment demographics, clinical symptoms, environmental factors, neuropsychological characteristics, genetic factors, and brain imaging characteristics could predict sleep side effects after methylphenidate (MPH) administration. They collected information on 83 ADHD patients, such as demographics, ADHD Rating Scale-IV (ADHD-RS) and Disruptive Behavior Disorder rating scales, neuropsychological tests [CPT, Stroop color word test], genetic and environmental variables (dopamine and norepinephrine receptor gene [DAT1, DRD4, ADRA2A, SLC6A2] polymorphisms, blood lead, and urine cotinine levels), and structural connectivity of fronto-striatal circuits. The resulting data were analyzed using three machine learning algorithms [logistic ridge regression (LR), SVM, J48]. The accuracy of predicting sleep problems was 95.5% for LR (AUC 0.99), 91% for SVM (AUC 0.85), and 90% for J48 (AUC 0.87). Inattentive symptoms in ADHD-RS, CPT response time variability, DAT1, ADRA2A, DRD4, SLC6A2 A3081T polymorphism and fronto-striatal structural connectivity were identified as the most differential features. Validation analysis showed an accuracy of 86.1% (AUC 0.92). This study suggested that multimodal classifiers, especially neuroimaging features, are helpful in predicting MPH side effects in ADHD children.

DISCUSSION

Machine learning and DL are among the most popular technologies of recent years, and meaningful results are constant-

ly being derived by combining them with neuroimaging. They have the advantage of overcoming limitations of traditional analytical methods by using previous mass-univariate statistics and enabling analysis of multivariate brain patterns and inter-regional correlations [45]. As described above, DL techniques provide significant diagnostic accuracy and results in detecting brain regions associated with disease, moving a step forward from traditional neuroimaging techniques. As multimodal approaches become easier with DL, opportunities to better implement the bio-psycho-social model of psychiatric disorders in clinical situations have opened up.

The combination of neuroimaging and DL is still a field that requires much caution and improvement. The first issue is the problem of overfitting. Overfitting refers to the problem of failing to form an appropriate algorithm due to excessive generalization that results from fitting to various types of data [46-48]. This is especially troublesome when the dataset is small [49], causing overestimations of accuracy [50-52]. The more features one needs to analyze, the more training data is required to avoid overfitting, further exacerbating the “curse of dimensionality.” Thus, there is a need to apply dimensionality reduction techniques such as principal components analysis or factor analysis in many machine learning studies [52]. In an attempt to overcome this difficulty, some studies have used methods such as regularization [53], early stopping [54], and drop out. [55]

The second issue is that, when using DL, bigger datasets result in more accurate algorithms, implying that the entire dataset will include all the images acquired in different ways (e.g., imaging tool, sites, etc.). In such cases, inadequate standardization can lead to inaccurate processing [56]. As a potential solution to this problem, a field called “brittle AI” is being studied and implemented.

The third problem is that of psychiatric classification. The diagnosis of psychiatric disorders is based on observed symptoms and signs, which can be an obstacle to prediction through DL. The training criteria for evaluating the accuracy of results obtained through DL also follow the current diagnostic classification system. Therefore, a new approach called the research domain criteria initiative [57] was devised to overcome the heterogeneity of psychiatric disorder. This is a method used to detect the brain circuits associated with shared symptoms and derive meaningful results for pathophysiology and etiology of psychiatric illnesses.

Finally, there is an overall lack of transparency and consequent interpretability from such experiments. Unlike general statistical analysis, it is difficult to intuitively recognize the results of analysis from the original data [58]. For example, it may be more difficult to detect abnormalities in specific brain regions of images from individuals using DL. This may be

due to a focus on features that are not clinically meaningful (e.g., artifacts) or a lack of information on treatment and/or developmental stages. Input modification methods [59] and deconvolution methods [60] are typically used to address this issue. Research that applies DL to neuroimaging analysis has been mainly conducted over the past 5 years and the field is still at an early stage. There are many research methods, such as targeting the entire brain area or a specific brain region, and each study utilizes various ANNs. Hence, there is great potential for development of the technique. In the future, after overcoming the above-mentioned limitations, DL can be used to discover a biomarker that distinguishes various psychiatric disorders and not just to distinguish between patient and NC groups. In addition, studies on the prediction of prognosis and treatment effects for neurodevelopmental disorders would be beneficial.

CONCLUSION

Neuroimaging studies of neurodevelopmental disorders have suggested various biomarkers; however, there are limitations in comprehensively analyzing such biomarkers to derive clinically significant results. Considering that the comorbidities of neurodevelopmental disorders are high, a new approach called DL can be applied to the clinical information extracted from currently available standardized diagnostic evaluations to improve the accuracy of diagnosis and better help clinicians in determining diagnosis and treatment.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jae-Won Song, Na-Rae Yoon, Bung-Nyun Kim. Data curation: all authors. Investigation: all authors. Project administration: Bung-Nyun Kim. Supervision: Bung-Nyun Kim. Validation: Bung-Nyun Kim. Writing—original draft: Jae-Won Song, Na-Rae Yoon, Soo-Min Jang, Ga-Young Lee. Writing—review & editing: Bungnyun Kim.

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