

A safety gate for automated DAT-SPECT interpretation: detection of atypical patterns

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Abstract

Background

Deep learning methods for automated interpretation of dopamine transporter (DAT) SPECT have shown excellent diagnostic performance but are often developed using research datasets that largely exclude patients with relevant vascular or structural brain lesions. Consequently, atypical DAT-SPECT patterns caused by such lesions and encountered in routine clinical practice may fall outside the intended operating domain of these algorithms and therefore require particular caution. We therefore aimed to develop a safety gate for automated DAT-SPECT interpretation by automatically identifying scans with atypical striatal binding patterns using routinely available semi-quantitative parameters.

Methods

A total of 1,860 consecutive clinical DAT-SPECT scans with [^{123}I]ioflupane acquired at a tertiary referral centre served as the training dataset. Visual assessment by five independent raters classified scans as atypical if at least three raters identified patterns suggestive of vascular or structural lesions. A classification and regression tree (CART) model with 10-fold cross-validation was developed to identify atypical scans using semi-quantitative binding ratios and derived parameters as candidate predictors. Generalizability was assessed in an independent out-of-distribution test dataset comprising 925 consecutive clinical DAT-SPECT scans acquired at a second centre using different hardware and reconstruction methods.

Results

Visual assessment detected atypical binding patterns in 15 of 1,860 (0.8%) scans in the training dataset and 4 of 925 (0.4%) scans in the out-of-distribution test dataset. The CART model retained hemispheric caudate binding ratio asymmetry ($200 \times |L - R| / (L + R)$) as the only predictor. A sensitive threshold (29.2%) on caudate asymmetry identified 80.0% (95%-confidence interval 51.9–95.7%) and 100% (39.8–100%) of atypical scans in the training and independent out-of-distribution test datasets, respectively, at a specificity of 99.0% (98.5–99.4%) and 99.0% (98.2–99.6%), respectively.

Conclusions

Atypical DAT-SPECT patterns potentially confounding automated interpretation are uncommon but occur regularly in routine clinical practice. A simple safety gate based solely on hemispheric caudate binding ratio asymmetry can identify these cases with high specificity. This pre-screening approach may improve the robustness and clinical applicability of automated DAT-SPECT interpretation by directing atypical scans to careful visual assessment, ideally together with structural imaging.

Background

Single-photon emission computed tomography (SPECT) with the dopamine transporter (DAT) ligand [^{123}I]ioflupane is widely used to detect or exclude loss of striatal DAT, a biomarker of nigrostriatal degeneration. It supports differentiation between neurodegenerative parkinsonian syndromes (with nigrostriatal degeneration) and secondary parkinsonism (without relevant nigrostriatal degeneration), as well as between dementia with Lewy bodies and Alzheimer's disease [1–7].

Recent years have seen considerable progress in the automated interpretation of DAT-SPECT, particularly through deep learning-based image analysis [8–10]. A growing number of studies have demonstrated that deep convolutional neural networks can classify DAT-SPECT scans with excellent diagnostic performance, often outperforming conventional semi-quantitative approaches [10, 11]. However, these algorithms are generally developed and validated using carefully curated research datasets that do not fully represent the spectrum of findings encountered in routine clinical practice [11].

One important difference between research datasets and routine clinical practice is the occurrence of atypical DAT-SPECT patterns caused by vascular or structural brain lesions. Major infarctions, lacunes, markedly enlarged perivascular spaces, cavernomas, and other lesions involving the striatum or substantia nigra may cause reductions of tracer binding that can confound detection versus exclusion of nigrostriatal degeneration [12–15]. Procedure guidelines therefore recommend joint interpretation of DAT-SPECT together with structural imaging [15, 16], which is part of the basic diagnostic work-up in patients with suspected neurodegenerative parkinsonian syndromes [17, 18]. In everyday clinical practice, however, sufficiently recent MRI or CT examinations are frequently unavailable at the time of DAT-SPECT interpretation, increasing the risk of lesion-related misinterpretation [19].

This discrepancy between research datasets and routine clinical practice may reduce the robustness of automated interpretation algorithms when applied in everyday clinical use. A practical strategy to address this challenge is to introduce a safety gate before automated interpretation. In the present study, the term safety gate refers to a pre-screening step that automatically identifies scans with atypical imaging patterns so that they can undergo careful visual assessment, ideally in conjunction with structural imaging, rather than routine automated interpretation.

To facilitate clinical implementation, such a safety gate should rely only on information routinely available in clinical practice such as binding ratios of [^{123}I]ioflupane in the striatum and its subregions [20–25].

Against this background, the aims of the present study were (i) to estimate the frequency of atypical DAT-SPECT patterns suggestive of vascular or structural lesions in routine clinical practice and (ii) to develop and validate a safety gate for automated DAT-SPECT interpretation based exclusively on readily available semi-quantitative parameters.

Methods

Training dataset

For the training dataset, the PACS of the University Medical Center Hamburg-Eppendorf was searched for all DAT-SPECT scans performed with [^{123}I]ioflupane in routine clinical practice between 2009 and 2025. A scan was included if (i) it had been acquired with a dual-head camera equipped with low-energy high-resolution or fan-beam collimators, and (ii) the raw projection data were available for consistent retrospective image reconstruction. No additional eligibility criteria were applied in order to preserve the heterogeneity of the routine clinical population.

This resulted in the retrospective inclusion of 1,860 consecutive clinical [^{123}I]ioflupane SPECT scans in the training dataset. The scans had been acquired with four different cameras according to common procedure guidelines after intravenous injection of 194 ± 21 MBq [^{123}I]ioflupane [15, 16, 26].

Image reconstruction was performed retrospectively using an ordered-subsets expectation-maximization algorithm with Chang attenuation correction, simulation-based scatter correction, and collimator–detector response modelling implemented in the Hybrid Recon-Neurology tool of the Hermes SMART workstation v1.6 [27].

Detailed acquisition and reconstruction parameters are summarized in Table 1.

Table 1

Acquisition and reconstruction parameters of the training and independent out-of-distribution (OOD) test datasets.

Site	Training dataset				OOD test dataset
	Hamburg				Freiburg
Camera	Siemens e.cam	Siemens Symbia TruePoint	Siemens Symbia TruePoint	Mediso AnyScan Trio (dual-head mode)	Siemens Intevo
Collimator	LEHR	LEHR	Fan-beam	LEHRHS	
# Scans	712	137	578	433	925
# Views	128	120	120	120	120
Scan arc [°]	180	180	180	180	180
Angular step [°]	2.81	3	3	3	3
Radius of rotation [mm]	165 ± 18	167 ± 19	153 ± 12	146 ± 11	148 ± 8
Matrix size	128x128	128x128	128x128	128x128	128x128
Pixel size [mm ²]	4.8x4.8	3.9x3.9	3.9x3.9	2.43x2.43	3.9x3.9
Energy window [keV]	147–171	147–171	147–171	143–175	147–171
Total net scan duration [min]	32–41	30–40	40	40	30
Reconstruction algorithm	OSEM (Hermes)				3DOSEM (Siemens)
# Iterations / # subsets	5/16	5/15	5/15	5/15	8/8
Corrections	Chang attenuation, simulation-based scatter correction, collimator–detector response modelling				CT-based attenuation correction
Postfiltering	3D Gaussian, 7 mm FWHM				3D Gaussian, 8 mm FWHM

Legend to Tab. 1: (FWHM = full-width-at-half-maximum, LEHR = low-energy-high-resolution collimator, LEHRHS = low-energy-high-resolution-high-sensitivity collimator, OSEM = ordered-subsets expectation-maximization)

Out-of-distribution test dataset

A total of 925 consecutive clinical [^{123}I]ioflupane SPECT scans with an auxiliary CT for attenuation correction from the University Medical Center Freiburg served as an independent retrospective out-of-distribution (OOD) test dataset. All scans had been acquired with a Siemens Intevo SPECT/CT system. Acquisition and reconstruction parameters are provided in Table 1.

Semi-quantitative analysis

Semi-quantitative analysis was performed in both datasets as described previously [26, 28]. In brief, individual [^{123}I]ioflupane SPECT images were spatially normalized to Montreal Neurological Institute template space using the Statistical Parametric Mapping software package (SPM12) and set of custom templates representing normal striatal binding and varying degrees of nigrostriatal degeneration-like reduction [26].

Binding ratio images were generated by voxel-wise scaling to the 75th percentile of voxel intensity in the whole brain as reference region excluding the striatum, thalamus, medial temporal lobe, brainstem, cerebellum, and ventricles [28].

Binding ratios were calculated for the caudate, putamen, and whole striatum using a hottest-voxels approach with large unilateral masks predefined in template space [10]. The number of hottest voxels corresponded to volumes of 5, 10, and 15 mL (625, 1250, and 1875 voxels of 2 mm edge length), approximating the anatomical volumes of the unilateral caudate, putamen, and striatum, respectively [29]. Unilateral putamen-to-caudate ratios were computed as well as left (L)-right (R) asymmetry indices for all parameters ($200 \times |L - R| / (L + R)$). To avoid numerical instability of the derived parameters by denominator values close to zero, all asymmetry indices and putamen-to-caudate ratios were calculated from binding ratios rather than specific binding ratios (binding ratio = specific binding ratio + 1).

Visual assessment

Visual assessment was based on a standardized display (Fig. 1) comprising ten transversal binding ratio slices (4 mm thickness) and one transversal binding ratio slab (12 mm thickness) [30]. Five raters with varying levels of experience independently evaluated all scans after standardized training. The raters were blinded to all demographic and clinical data. The scans from training and test datasets were presented together in randomized order.

Each scan was categorized as either atypical or typical. Atypical patterns included striatal signal reductions suggestive of vascular or structural lesions, such as predominant caudate involvement or more or less complete loss of striatal signal in one hemisphere alongside relatively preserved striatal signal in the other. Typical patterns included normal scans and scans with nigrostriatal degeneration-like

reduction. A rather uniform (global) reduction in striatal signal, with more or less complete delineation of the striatum bilaterally and without posterior putamen predominance, was also considered typical.

Statistical analysis

The majority vote across raters served as the reference standard, that is, scans were classified as atypical if ≥ 3 of the five raters assigned this label. All other scans were classified as typical.

Differences in image characteristics between datasets were assessed by comparing the distribution of the putamen binding ratio (minimum of both hemispheres) using a Gaussian mixture model approach [26]. Atypical cases were excluded from this analysis.

In the training dataset, univariate analyses compared semi-quantitative parameters between atypical and typical scans using heteroscedastic t-tests. Parameters with $p < 0.001$ (uncorrected for multiple comparisons) were entered into a classification and regression tree (CART) model.

The CART model minimized Gini–Simpson impurity, was restricted to a maximum depth of 2 and used a 10-fold higher misclassification cost for atypical cases than for typical cases. Ten-fold cross-validation was used to avoid overfitting in the training dataset.

Model performance was assessed by sensitivity and specificity, separately in the training and OOD test datasets.

Results

Training dataset

Among the 1,860 DAT-SPECT scans in the training dataset, 7 were rated as atypical by 4 raters, 8 by 3 raters, and 8 by one rater. The remaining 1,837 scans were not rated as atypical by any rater. Accordingly, 15 scans (0.8%) were classified as atypical by majority vote (Fig. 2), whereas the remaining 1,845 (99.2%) were classified as typical.

Atypical and typical DAT-SPECT scans did not differ significantly with respect to patient sex (40.0% vs. 42.8% females, Pearson chi-square $p = 0.828$) or age (69.9 ± 11.2 y vs. 66.9 ± 11.4 y, heteroscedastic t-test $p = 0.322$).

Out-of-distribution test dataset

Among the 925 scans in the OOD test dataset, 1 was rated as atypical by all raters, 2 by 4 raters, and 1 by 3 raters. Eight scans were rated as atypical by one rater only. Accordingly, 4 scans (0.4%) were classified as atypical by majority vote (Fig. 3), whereas the remaining 921 (99.6%) were classified as typical.

Atypical and typical DAT-SPECT scans in the OOD test dataset did not differ significantly with respect to patient sex (25.0% vs. 40.9% females, $p = 0.518$) or age (69.3 ± 8.5 y vs. 68.4 ± 10.4 y, $p = 0.862$).

Dataset comparison

Gaussian mixture modelling of minimum putamen binding ratio distributions demonstrated differences between the training and independent test datasets (Fig. 4). Specifically, putamen binding ratios were consistently higher in the training dataset, with the largest difference observed for scans with normal striatal binding.

Candidate predictors

The following 8 parameters differed significantly between atypical and typical scans in the training dataset at the predefined significance threshold of uncorrected $p < 0.001$ and were therefore retained as candidate predictors for CART modelling: minimum whole striatum binding ratio, minimum caudate binding ratio, mean and maximum of the putamen-to-caudate ratio and all four asymmetries (caudate, putamen, whole striatum, and putamen-to-caudate ratio). All other parameters were excluded.

Development of the safety gate

Although 8 semi-quantitative parameters fulfilled the predefined selection criterion, CART retained only hemispheric caudate binding ratio asymmetry in the final model (Fig. 5). The first split used a caudate binding ratio asymmetry threshold of 41.4%. Of the nine scans exceeding this threshold, eight (88.9%) were atypical whereas one (11.1%) was classified as typical according to the visual reference standard. The 41.4% threshold is referred to as the “specific” cut-off in the following.

For cases below the specific threshold on the caudate asymmetry, the CART introduced a second split, again using the caudate asymmetry, but with a lower threshold of 29.2%. Of the 21 scans exceeding this threshold, 4 (19.0%) were atypical whereas the other 17 (81.0%) were typical. The 29.2% threshold is referred to as the “sensitive” cut-off in the following.

Performance of the safety gate

The performance of the proposed safety gate, the hemispheric caudate binding ratio asymmetry, is summarized in Table 2. The specific cut-off achieved a specificity of almost 100% in both datasets, whereas the sensitive cut-off increased sensitivity while maintaining a specificity of approximately 99%.

Table 2
Performance of the proposed safety gate.

dataset	Cut-off	Sensitivity (%)	Specificity (%)
Training	Specific	53.3 (26.6–78.7)	99.9 (99.7–100)
Training	Sensitive	80.0 (51.9–95.7)	99.0 (98.5–99.4)
Test	Specific	75.0 (19.4–99.4)	99.9 (99.4–100)
Test	Sensitive	100 (39.8–100)	99.0 (98.2–99.6)
Legend to Table 2: Sensitivity and specificity for the identification of atypical cases using the specific or the sensitive cut-off on the asymmetry of the caudate binding ratio. 95%-confidence intervals are given in parentheses. (Specific cut-off: 41.4% caudate binding ratio asymmetry. Sensitive cut-off: 29.2% caudate binding ratio asymmetry)			

Overall, the proposed safety gate showed similar performance in both the training and independent OOD test datasets, supporting the robustness of the selected decision rule across different imaging settings.

Discussion

The present study proposes a safety gate for automated DAT-SPECT interpretation based on a routinely available semi-quantitative parameter. The safety gate addresses the problem of atypical DAT-SPECT patterns that may be caused by vascular or structural brain lesions and can confound scan interpretation.

The need for such a safety gate arises from the increasing use of *automated* image interpretation in DAT-SPECT [11]. Deep learning algorithms achieved excellent performance in the detection of nigrostriatal degeneration based on DAT-SPECT and are therefore likely to become integrated into clinical workflows [8–10, 31, 32]. However, like all supervised machine learning methods, their performance depends on the similarity between the data used for development and the data encountered during clinical application. Research datasets commonly used for algorithm development intentionally exclude patients with clinically relevant vascular or structural abnormalities identified on structural imaging [11]. Consequently, atypical DAT-SPECT patterns caused by such lesions are likely to be underrepresented compared with routine clinical practice. The proposed safety gate addresses this discrepancy by identifying scans that should be diverted from routine automated interpretation to careful visual assessment, ideally in conjunction with structural imaging.

Only hemispheric caudate binding ratio asymmetry was retained in the final CART model, although several semi-quantitative parameters differed significantly between atypical and typical scans. To some extent, this finding is consistent with the definition of atypical patterns used for visual assessment, which explicitly included predominant caudate involvement as one of the characteristic imaging features. Nevertheless, the selection of caudate asymmetry also appears plausible from a pathophysiological perspective, as nigrostriatal degeneration in Parkinson's disease and atypical

neurodegenerative parkinsonian syndromes typically follows a pattern with posterior putaminal predominance and progressive bilateral involvement, whereas vascular or structural lesions frequently produce abrupt and unilateral reductions of tracer binding. The fact that none of the other semi-quantitative parameters provided additional information beyond caudate asymmetry suggests that this single measure captured most of the information required for identifying atypical patterns in the present dataset.

The proposed safety gate was additionally evaluated in an independent out-of-distribution test dataset. This test dataset differed from the training dataset with respect to scanner hardware, attenuation correction, reconstruction methodology, which resulted in different distributions of putamen binding ratios, representing realistic inter-centre variability encountered in clinical practice. Nevertheless, the same decision thresholds maintained very similar diagnostic performance. This may be explained by the use of an asymmetry index rather than absolute binding ratio values. Absolute binding ratios are known to be sensitive to technical variability related to SPECT hardware, acquisition protocols, and reconstruction methods [20, 28, 33, 34]. By contrast, asymmetry measures are based on within-subject comparisons between hemispheres and are therefore less sensitive to global scaling effects and inter-site variability. They are also less dependent on age and sex than absolute binding ratios [24].

Although atypical DAT-SPECT patterns were uncommon, they are clinically relevant because DAT-SPECT is typically performed at the end of the diagnostic pathway in patients with clinically uncertain parkinsonian syndromes. Consequently, imaging findings may substantially influence diagnosis and patient management.

The observed prevalence of atypical DAT-SPECT patterns is plausible based on structural imaging studies. In a community-based cohort, approximately 18% of stroke-free subjects showed subclinical brain infarctions on MRI, with the basal ganglia being the most frequently affected region, accounting for approximately 30% of all subclinical infarctions [35]. Thus, about 5% of subjects exhibited subclinical infarctions in the basal ganglia. The true prevalence of striatal lesions potentially relevant for DAT-SPECT interpretation may therefore be higher than the $\leq 1\%$ observed in the present study. Smaller lesions, lesions producing more typical patterns of striatal signal reduction, or patients not referred for DAT-SPECT because structural imaging had already demonstrated a possibly causative lesion may all contribute to underestimation.

A methodological aspect of the present study is the calculation of asymmetry indices from binding ratios rather than *specific* binding ratios. This approach avoids numerical instability when specific binding ratios approach zero while preserving the interpretation of the asymmetry index.

The present study has several limitations. First, the reference standard was based on consensus visual assessment rather than systematic correlation with structural imaging. However, the objective of the proposed safety gate was not lesion detection itself but identification of scans requiring particular caution during automated interpretation. Second, the number of atypical scans was small, resulting in wide confidence intervals for sensitivity estimates despite the large overall study population. Third, head

rotation, head tilt, or other acquisition-related factors may also increase hemispheric asymmetry and thereby contribute to false-positive classification. However, head rotation or head tilt may also affect automated interpretation and therefore represent scans for which additional visual review appears appropriate. Finally, the present work focused exclusively on atypical striatal patterns and did not consider extrastriatal abnormalities that might also influence automated image analysis.

Conclusions

The present study suggests that hemispheric caudate binding ratio asymmetry, a routinely available semi-quantitative parameter, can be used to identify atypical DAT-SPECT patterns. Such a safety gate may complement automated DAT-SPECT interpretation by identifying scans that require careful visual assessment before automated classification.

Abbreviations

CART = classification and regression tree, **DAT** = dopamine transporter, **L** = left, **OOD** = out-of-distribution, **R** = right, **SPECT** = single-photon emission computed tomography

Declarations

Ethics approval and consent to participate: Waiver of informed consent for the retrospective analysis of the anonymized clinical data was obtained from the ethics review board of the general medical council of the state of Hamburg, Germany (reference number 2021-10455-BO-bet). All procedures performed in this study were in accordance with the ethical standards of the ethics review board of the general medical council of the state of Hamburg, Germany, and with the 1964 Helsinki declaration and its later amendments.

Consent for publication: Not applicable.

Availability of data and materials: All results of semi-quantitative analysis and visual assessment are available for research purposes upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: All authors contributed to the conception, design and collection of data (IA, TB, MP, LB, AM, SK, RBr, PTM, RBu). IA, TB, PTM and RBu performed the analyses and wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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were made by the human

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Figures

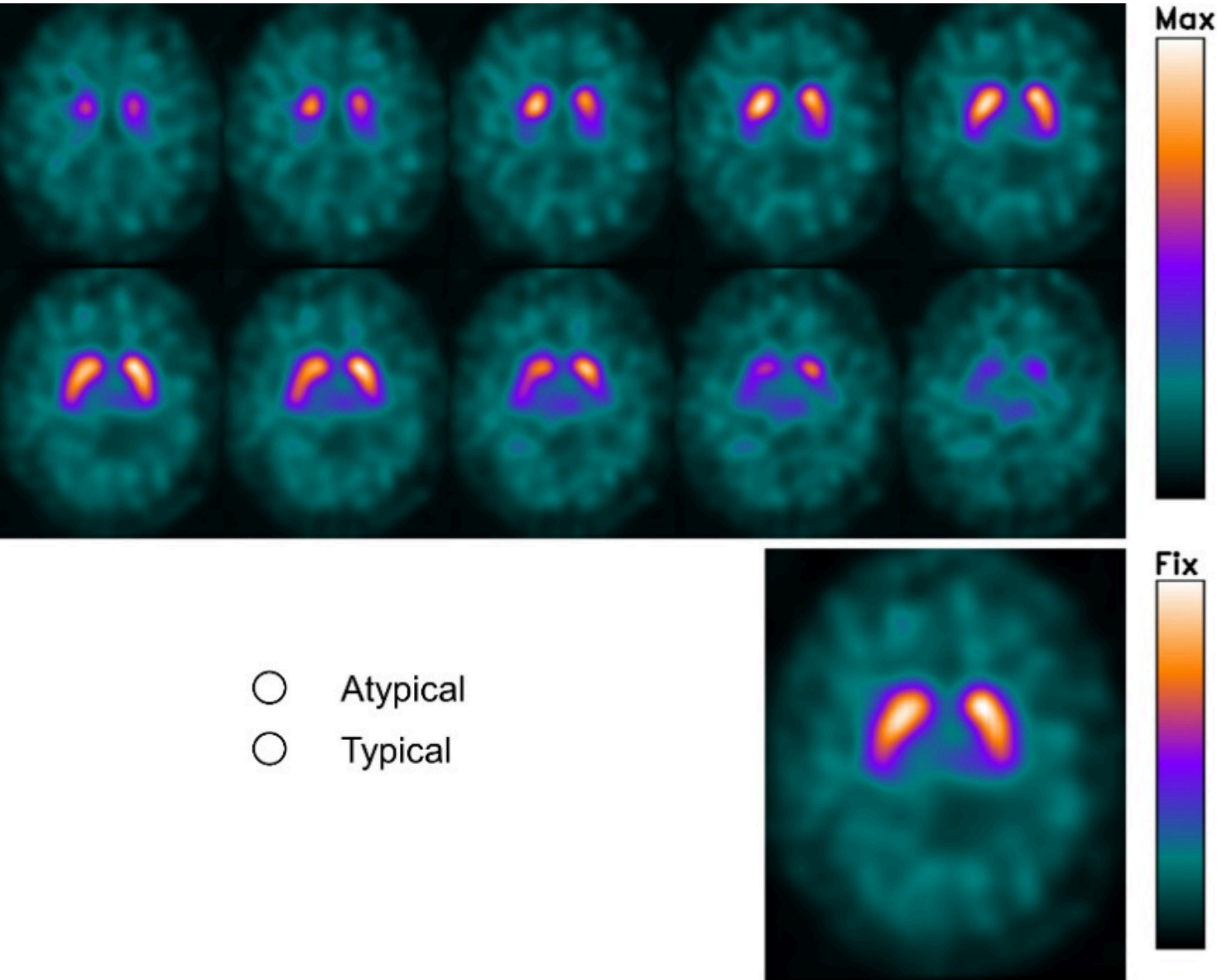


Figure 1

Standardised display for visual assessment.

Legend to Fig. 1: Ten binding ratio slices (4 mm thickness) are shown in the upper panel. For “Max” scaling, the upper limit of the color table is set to the individual maximum voxel value in the brain. As a consequence, the maximum is always displayed in the maximum color (here, white). The lower limit is set to 0 (no background subtraction). The lower panel shows a 12 mm binding ratio slab with “Fix” scaling of the color table (the same upper limit for all subjects), resulting in consistent extrastriatal background intensity across subjects. The Max and Fix scaling combination for the standardised display can replace the need for manual color table adjustment.

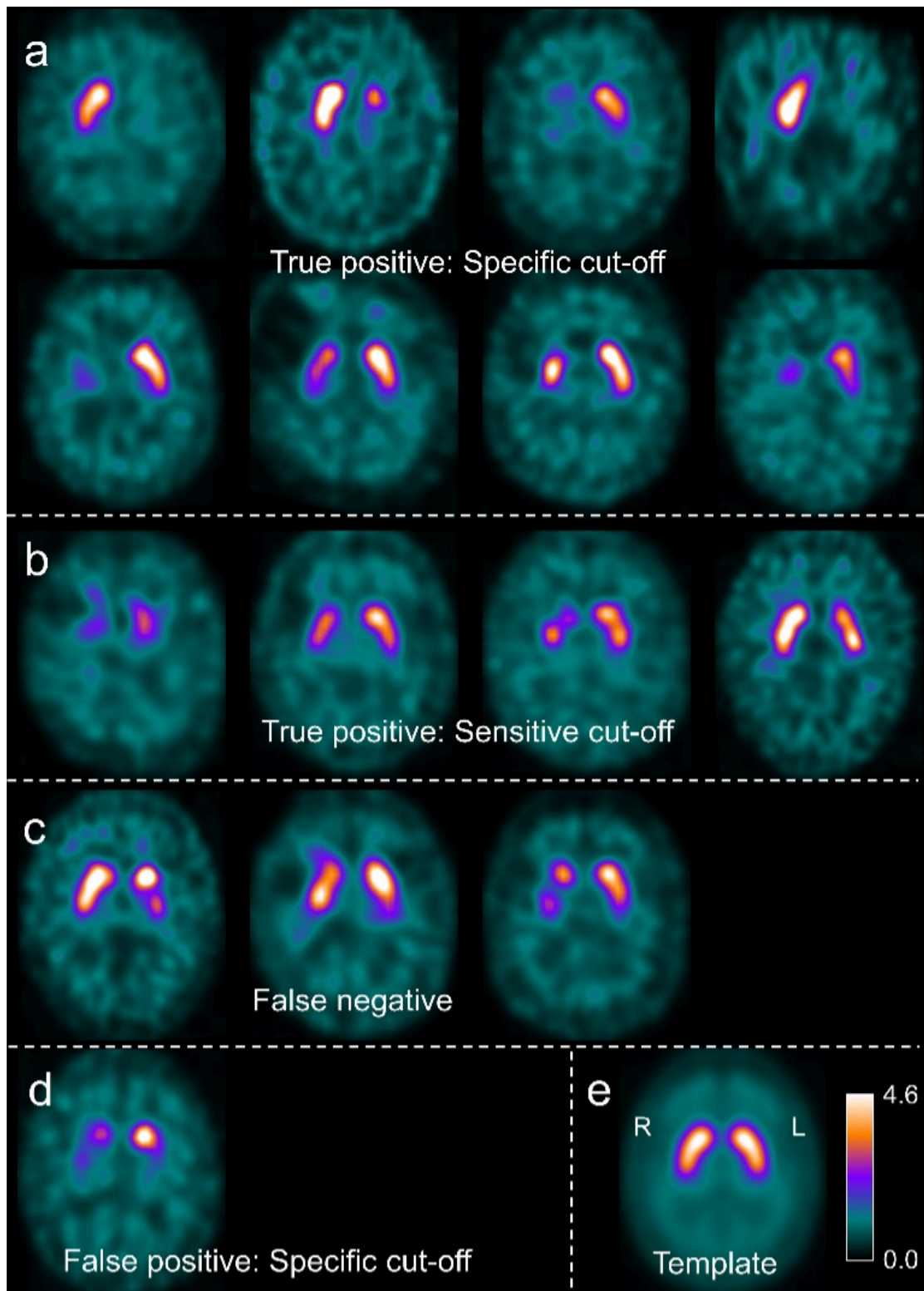


Figure 2

Performance of the proposed safety gate in the training dataset.

Legend to Fig. 2: (a-c) Binding ratio slab (12 mm) of the 15 atypical cases in the training dataset. (a) Eight of these cases were correctly identified as atypical by the *specific* cut-off on the asymmetry of the caudate binding ratio. (b) The *sensitive* cut-off on the asymmetry of the caudate binding ratio correctly

identified four additional cases. **(c)** The remaining 3 atypical cases were not detected by asymmetry of the caudate binding ratio, even when using the sensitive cut-off. **(d)** There was a single false positive case classified as atypical by the specific cut-off on the asymmetry of the caudate binding ratio that was typical according to the visual reference standard. The 17 false positive cases classified as atypical according to the sensitive, but not the specific, cut-off on the asymmetry of the caudate binding ratio are shown in Supplementary Figure 1. **(e)** DAT-SPECT template.

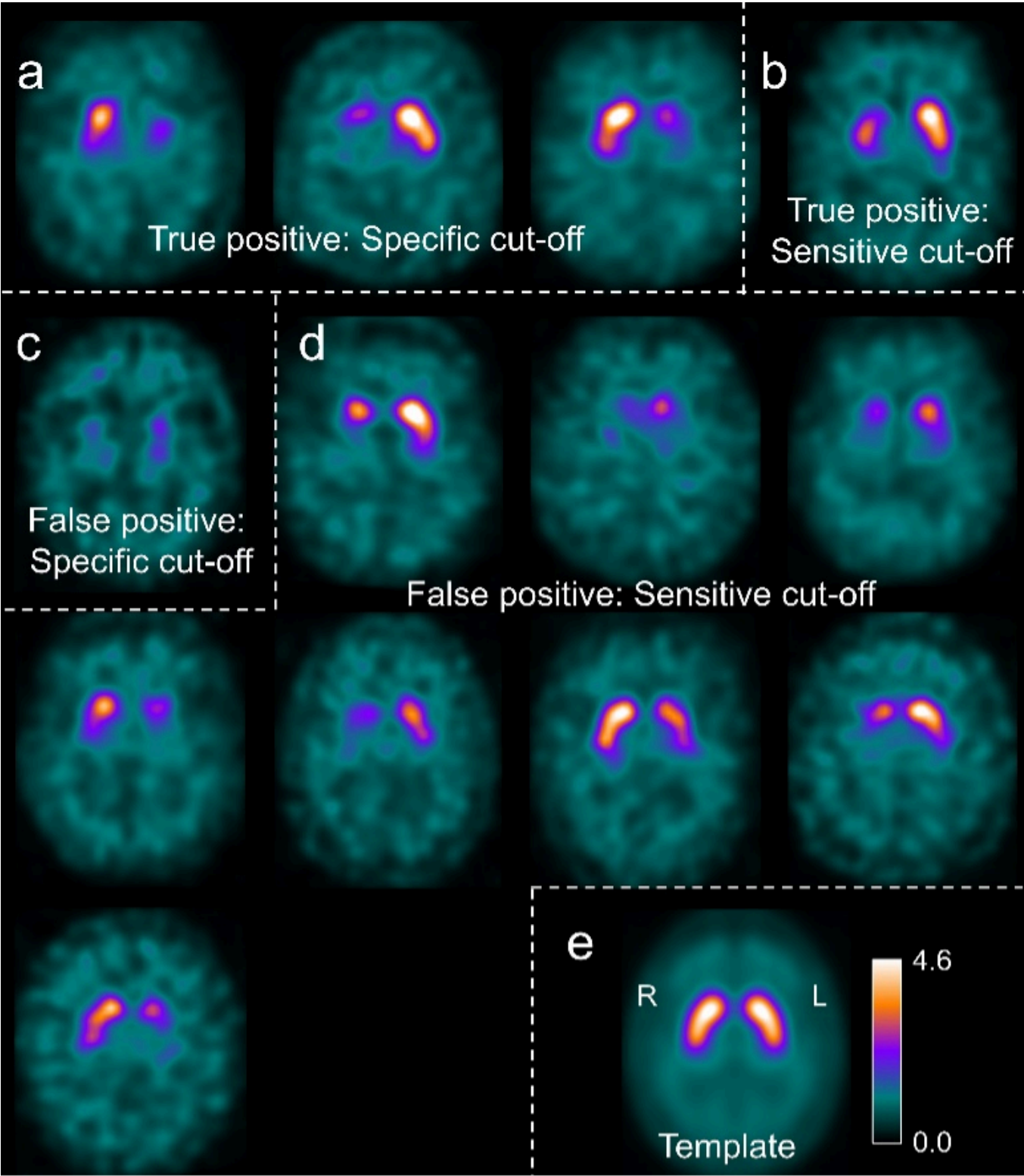


Figure 3

Performance of the proposed safety gate in the independent out-of-distribution test dataset.

Legend to Fig. 3: (a-b) Binding ratio slab (12 mm) of the 4 atypical cases in the test dataset. **(a)** Three of these cases were correctly identified as atypical by the *specific* cut-off on the asymmetry of the caudate binding ratio. **(b)** The *sensitive* cut-off on the asymmetry of the caudate binding ratio correctly identified the remaining cases. There were no false negative cases in the test dataset. **(c)** There was a single false positive case classified as atypical by the specific cut-off on the asymmetry of the caudate binding ratio that was typical according to the visual reference standard. **(d)** Eight additional false positive cases were atypical according to the sensitive, but not the specific, cut-off on the asymmetry of the caudate binding ratio. **(e)** DAT-SPECT template.

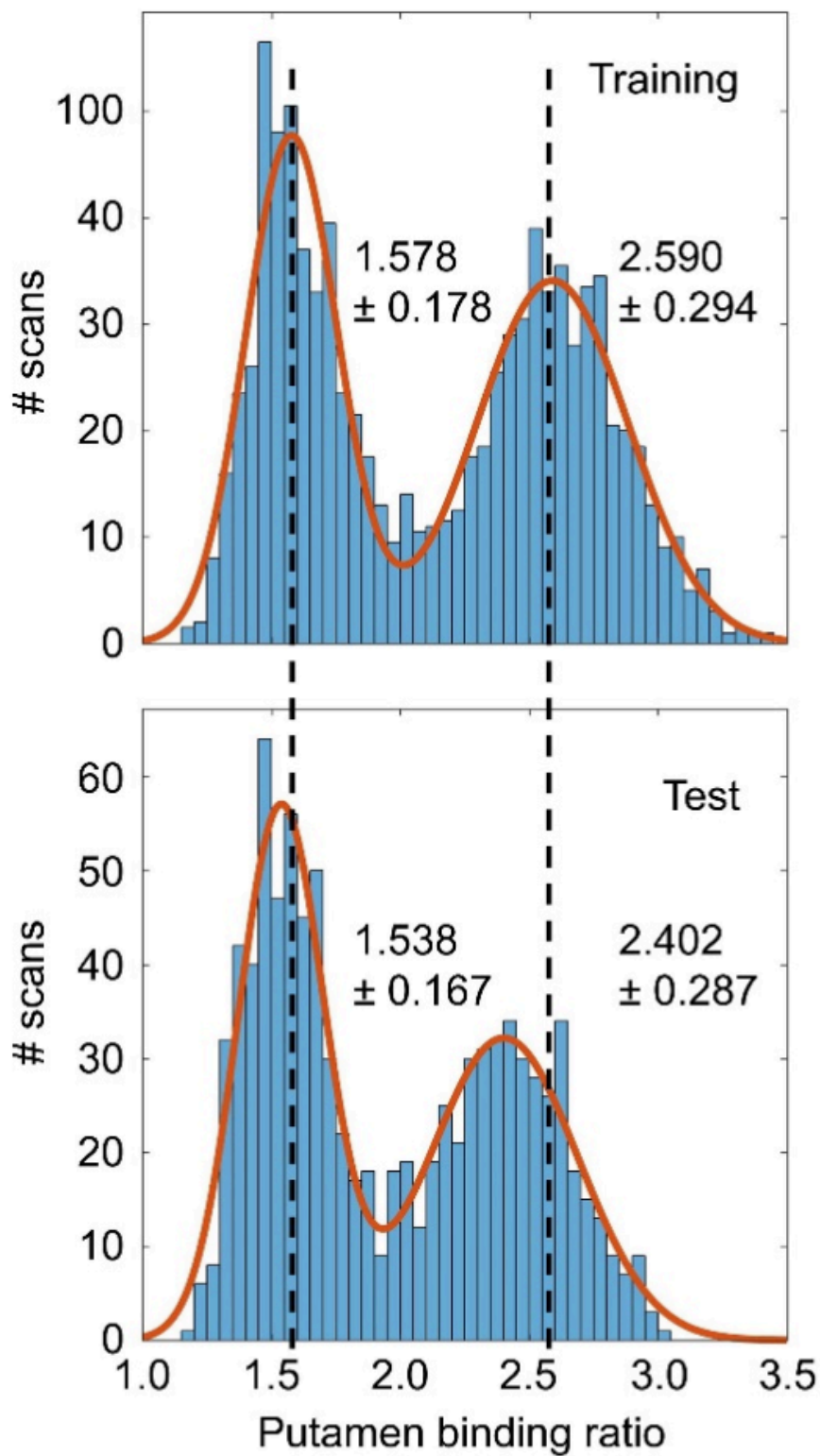


Figure 4

Comparison of putamen binding ratio distributions between datasets.

Legend to Fig. 4: Histograms of minimum putamen binding ratio in training (top) and test (bottom) datasets with Gaussian mixture model fits (orange lines). The numbers specify mean $\pm$ standard deviation of reduced and normal putamen binding ratio according to the fits.

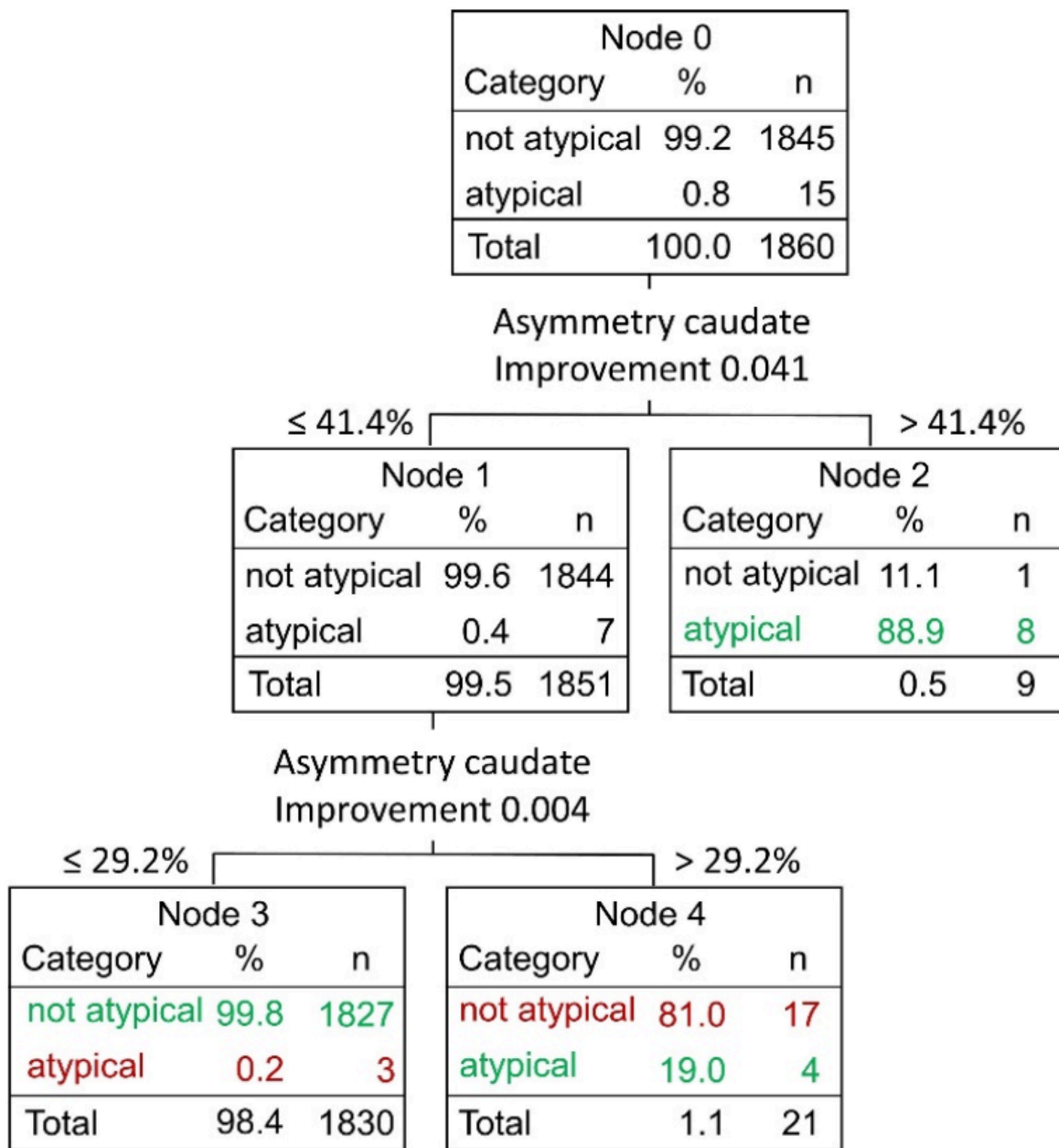


Figure 5

Development of the proposed safety gate.

Legend to Fig. 5: Classification and regression tree model to identify atypical DAT-SPECT in the training dataset. Correct classifications in green, misclassifications in red.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFig.docx](#)