Judged by your neighbors: A novel framework for personalized assessment of brain structural aging effects in diverse populations

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Abstract

Despite their promise, current neuroimaging biomarkers often fail to capture the full spectrum of inter-individual variability in brain structure and aging effects. This limits their ability to detect subtle norm deviations and impacts their utility for personalized care. We introduce Nearest Neighbor Normativity (N^3), a novel framework designed to resolve the confound between natural diversity and subtle pathological patterns. It evaluates individual brain structures from several meaningful viewpoints, accommodates a variety of co-existing normative prototypes and accounts for individually varying progression rates of brain structural decline. Using MRI data of 36,896 individuals, we provide empirical evidence that the N^3 biomarker effectively disentangles natural inter-individual variability from pathological alterations, significantly outperforming brain age models and traditional normative modeling approaches in the detection of neurodegenerative diseases. The N^3 framework is easily adaptable to various medical domains, fostering individualized and context-rich biomarkers and paving the way for more targeted and personalized therapeutic strategies.

Keywords: Normative Modeling, Precision Medicine, Diversity, Brain Age, Density-Estimation

1 Introduction

Neuroimaging biomarkers hold the promise to transform psychiatric research by providing objective measures that can move the field beyond symptom descriptions [1–6]. Neuroimaging biomarkers are closely tied to the concept of brain structural normativity, i.e. the degree of alignment with expected norms seen in the general population. Despite established consensus about the individuality in brain structure, current

biomarker assessments heavily rely on population averages and inherently exclude the possibility of multiple, equally viable normative patterns. The pursue of precision medicine requires to shift away from group averages and tailor medical interventions to individual physiology [7, 8]. In fact, finding (subtle) individual anomalies moderates our ability to diagnose and treat diseases effectively and is a practical necessity for the personalization of patient care. Redefining neuroimaging biomarkers to better account for the population-inherent diversity is thus not merely an academic exercise, but holds profound implications for medical practice.

Two prominent approaches have emerged in the search for reliable neuroimaging biomarkers in brain structure thus far. The first approach, called Brain Age [9, 10], trains machine learning models to predict chronological age from brain structure using examples of a healthy reference sample. The goal is to detect unusual brain structural decline in unseen samples. The resulting biomarker, the Brain Age Gap (BAG), is defined as the difference between chronological and predicted age and has been statistically associated with numerous neurological and psychiatric conditions, such as Alzheimer's Disease (+5-10 years), Mild Cognitive Impairment, (+1-10 years), Major Depressive Disorder (BAG 1-4 years), Schizophrenia (+3-12 years). [11–15].

However, the BAG's ability to capture individual norm deviations is naturally limited due to the multifaceted nature of individual aging processes. How quickly aging effects progress in individuals is highly variable and a complex interplay of genetic predisposition, behavioral choices and cumulative impact of various adverse or protective exposures [16–20]. This unique combination of factors inevitably results in different aging effects seen among same-aged individuals. Using chronological age to assess normative neurodegeneration thus inherently lacks precision. Consequently, the resolution of the BAG as a personalized brain structural assessment tool is limited and its utility mainly constrained to group comparisons.

The second prominent approach towards a brain structural biomarker emerges from so-called normative modeling [21]. Normative modeling uses statistical distributions to quantify brain structural measures in relation to the population average and the variance around it [22]. It has been successfully applied to detect brain structural norm deviations in various psychiatric disorders [23]. By design, normative models interpolate natural variability into a single reference distribution, centered around the population average. This mean-centric framework neglects the heterogeneity of physiological manifestations and does not account for biologically valid alternative norms. Thus, these population-wide, and often univariate, models risk masking subtle details that are critical for obtaining nuanced individual clinical insights [24].

To address the methodological shortcomings of the approaches described above, we propose a novel normativity estimation framework called Nearest Neighbor Normativity (N^3). It uses four core strategies to better understand an individual brain structure within the natural diversity of the population.

Demographic contextualization.

First, it evaluates brain structures in relation to demographically matched subgroups to reduce confounding variability. We hypothesize that this narrower comparison enables the detection of nuanced deviations often overlooked in broader models.

Multinorm accommodation.

Second, the N³ framework avoids comparisons to the population average and instead accommodates a variety of normative brain structural prototypes per age-group. Methodologically, this can be expressed with straightforward and distribution-free local density estimation techniques such as the Nearest Neighbor Algorithm [25].

Normativity profiles.

Third, each individual receives a so-called normativity profile, which joins multiple evaluations from different meaningful viewpoints into an comprehensive overview. In particular, it quantifies how an individual's brain structure aligns with expected patterns across the aging continuum, positioning it within the spectrum of aging effects (see Figure 2).

Clinically adaptable metric.

Fourth, an analysis of the normativity profile distills its context into a single metric which we call the N³ biomarker. The N³ biomarker expresses how common a normativity profile appears in relation to a particular clinical subgroup. In this work, we use the N³ biomarker to express the typicality of aging effects seen in an individual brain structure for a particular age group. Nevertheless, clinicians can adapt this metric to specific goals, for example, to identify typical profiles associated with high treatment response.

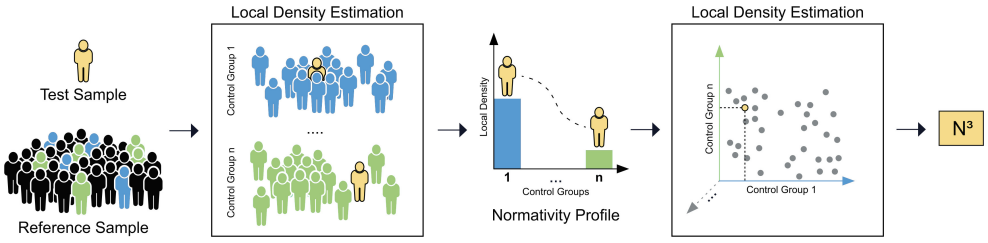

Fig. 1 Our proposed N³ framework entails methodological innovations that refine normativity assessments in large and diverse medical datasets. Here, we apply it to brain structure to foster the detection of pathological norm deviations amidst neuroanatomical variablility and individual progression rates in aging-related decline. The N³ entails four key strategies. First, we propose to use several carefully tailored control groups to promote the detection of subtle and nuanced anomalies that may escape broader comparative models. Second, we refrain from comparisons to a single normative tendency such as the population average. Instead, we propose to quantify normativity assessment with local density estimation algorithms, which effectively embraces diversity and acknowledges the possibility of multiple, equally viable health states in the population. Third, we introduce global context to the normativity assessments and join multiple comparative normativity estimations per individual into a so-called normativity profile. This normativity profile acts as a holistic representation of a patient's health status and provides a multifaceted contextualization to the complex and heterogeneous nature of medical observations. Fourth, we convert the normativity profile into a singular, actionable metric, which we call N³. It synthesizes the accumulated information of prior steps and can be adapted to a variety of clinical inquiries. For example, the final N³ normativity assessment can be fine-tuned to express normativity in relation to specific clinical outcomes. In the example of brain structure, normativity profiles can for example be compared to those of patients who exhibit high treatment response. The N³ approach is universally applicable, and we see great potential that its application will advance normativity assessments and contribute to personalized patient care.

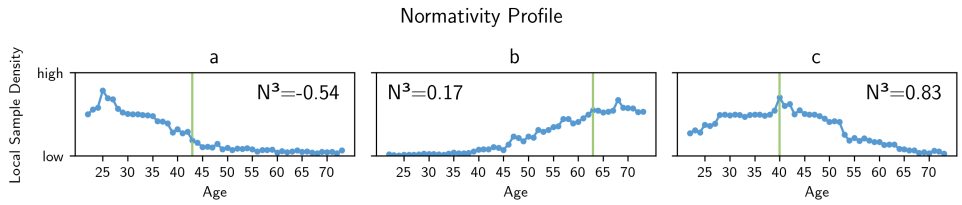

Fig. 2 Individual brain structural normativity profiles of three exemplary individuals of the training sample (see Methods 1 and 2). The normativity profile shows a brain structure's level of coherence with different reference samples along the age continuum (blue). Chronological age is depicted in green. The N^3 framework compares aging effects of a particular brain structure to expected aging patterns of different age groups along the age continuum. Moreover, the use of local density estimation technique enables several normative prototypical brain structures per age bin and is able to capture varying, yet normative rates of aging-related decline. a) An individual's brain structure aligns with younger brain structures, indicating fewer aging effects as commonly seen in same-aged individuals b) An individual brain structure aligns with older brain structures, indicating premature neurodegeneration processes. c) A brain structure exhibits high alignment within its own age group and shows deprecating alignment within other age groups.

In summary, the N^3 approach addresses a key concern in neurological research, namely the challenge of distinguishing inter-individual variability in healthy brain structural decline from pathological norm deviations. By providing a more comprehensive and context-rich assessment of individual brain structures, the N^3 is inherently designed to improve the understanding of neuroanatomical diversity and the detection of unusual patterns. We benchmark the efficacy of the N^3 framework relative to conventional neuroimaging biomarkers. To this end, we use neurodegenerative diseases as model diseases to represent brain structural alterations and pathological norm deviations. We show that, indeed, the N^3 biomarker enables enhanced understanding of the heterogeneous and complex neuroanatomical variability and individual pathological norm deviations.

2 Results

All normative models are trained with neuroimaging data from T1-weighted MRI scans of 29,883 individuals of a large population-based study and evaluated in 7,013 individuals with varying levels of neurodegeneration from different study populations (see Methods 2). Our analysis focuses on gray matter (GM), white matter (WM), hyperintense white matter (WMH), total intracranial volume (TIV) and cerebrospinal fluid (CSF) volumes. These global measures provide a comprehensive overview of brain structure[26]. We use these broad aggregates of complex physiological features to represent typical clinical measurements, and verify the algorithm's efficacy to derive meaningful disease indicators from these global parameters.

We evaluate the N^3 marker efficacy against conventional normative modeling approaches. Using classical normative modeling [21, 23], we derive two normativity scores, the first being the sum of the absolute z-scores (NM-S), the second counting the number of z-scores whose magnitude deviates beyond a threshold of ± 1.96 (NM-C). We also benchmark our approach against the Brain Age paradigm, which utilizes a

machine learning model to predict chronological age from brain structural data[9, 11]. Deviations between predicted and actual age, referred to as the Brain Age Gap (BAG) indicate neurodegenerative alterations (for details please refer to Methods Section 1, 3 and 4)

Applying the normative models to evaluate brain structure of both cognitively healthy and diseased individuals, we validate the ability of each biomarker to differentiate between healthy inter-individual variability and (early) states of pathological decline. To this end, instances of Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD) serve as model diseases to represent brain structural alterations and pathological norm deviations.

2.1 Increased statistical explanatory power in distinguishing neurodegenerative diseases

First, we assessed the statistical power of each biomarker, specifically examining the extent to which the marker detects unusual pattern deviations in group-level analyses. We calculated the effect size (partial eta squared, η^2) for the classification of healthy individuals from those affected by disease (MCI, AD or FTD, respectively; see Methods 5.5). Post-hoc comparisons then enabled us to evaluate which biomarker was able to provide the most statistical power. The $\mathbf{N^3}$ marker consistently showed higher discriminative ability across all neurodegenerative conditions compared to other markers used in the study (see Figure 3 and Table 1).

For AD, the $\mathbf{N^3}$ biomarker showed the largest effect size (η^2= 0.29), signifying that approximately 29% of the variability can be explained by differences in the $\mathbf{N^3}$ marker levels between the AD group and controls. In the context of FTD, all markers demonstrated large effect sizes, while the $\mathbf{N^3}$ stood out with an effect size of $\eta^2 = 0.38$. The results for Mild Cognitive Impairment (MCI) differed, as all markers showed generally lower explanatory power. Nonetheless, the $\mathbf{N^3}$ marker displayed a relative advantage, with an effect size of $\eta^2 = 0.07$, compared to $\eta^2 = 0.05$ for the Brain Age Gap (BAG) and $\eta^2 = 0.02$ for the normative modeling scores. Overall, the results suggest $\mathbf{N^3}$'s enhanced capability of discerning the subtle and complex neurostructural alterations associated with different stages of pathological decline in group level analysis.

2.2 Improved personalized predictions

Second, we conduct machine learning analyses to evaluate each biomarker's utility in predicting the occurrence of a neurodegenerative disease on a single-subject level. Machine learning models transcend conventional statistical models by handling multivariate and non-linear relationships and shifting the focus from group average comparisons to predictions on an individual level[27]. We employ cross-validation strategies, which systematically tests each marker against new, unseen data to verify the accuracy, robustness, and generalizability of the models. Such validation is imperative to ensure reliability when these markers are applied in clinical environments [28]. The performance of the machine learning models is quantitatively evaluated using metrics such as sensitivity, precision, balanced accuracy, and the F1-score —each providing a different lens through which to assess clinical utility. Balanced accuracy provides a

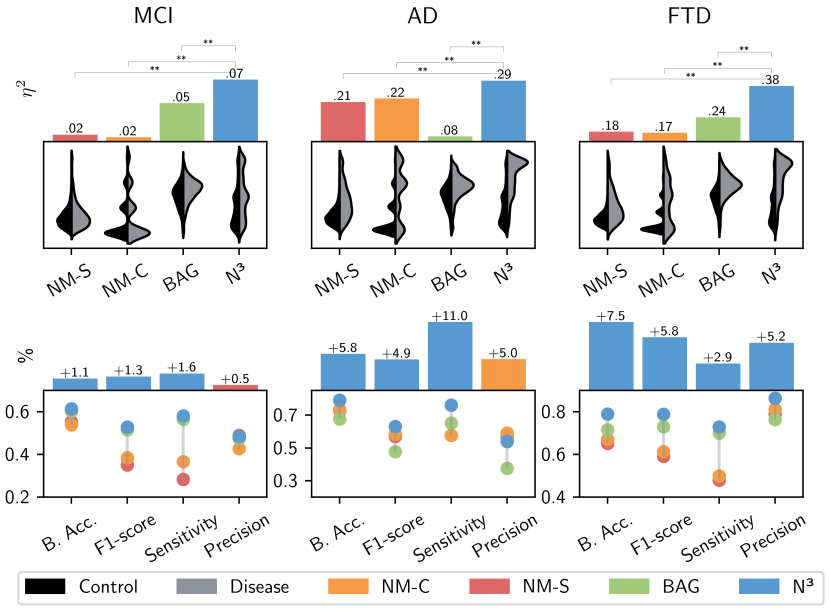

Fig. 3 **Top**: The top panel shows the results of the statistical analyses. Statistical effect sizes (partial eta squared - η^2) are given for the different biomarkers (N³ - our approach, NM-S - the sum of the absolute z-scores, NM-C - the number of z-scores whose magnitude deviates beyond a threshold of ±1.96, and the BAG - Brain Age Gap). We evaluate each normative modeling approach's ability to parse inter-individual variability and detect pathological alterations. For each marker, we test the ability to differentiate between controls and diseased individuals in group-level analyses, using neurodegenerative diseases as representative models of adverse norm deviations and pathological patterns. Results are given for Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), and Frontotemporal Dementia (FTD), respectively. Post-hoc comparisons of the effect sizes revealed larger explained variance of our N³ marker in all neurodegenerative conditions. The level of significance in the differences between the η^2 of N³ and η^2 of the other normativity estimation approaches is indicated above. Significance was confirmed through permutation testing using 1000 random permutations. The distribution plots below show each marker's value distributions for healthy controls (black) and diseased individuals (gray). **Bottom**: We use machine learning to evaluate the expressiveness of each biomarker on a single-subject level. The N³ marker demonstrated increased accuracy in predicting the occurrence of pathological norm deviations, in this case the presence of neurodegenerative diseases for individual patients. We show the different marker's performance metrics [balanced accuracy (B.Acc), F1-Score, Recall and Precision] and the performance advantage of the best marker in relation to the second best marker in percentage (above).

holistic view, ensuring that both the presence and absence of disease are accurately identified. Sensitivity is particularly critical in a clinical setting as it measures the model's capability to capture as many diseased patients as possible, thus effectively measuring a biomarker's utility as a screening tool. Complementary precision ensures that the majority of patients identified by the model as having a disease truly have the disease. The F1-score is crucial for its balance of precision and sensitivity—a vital feature to avoid unnecessary interventions or over-treatment or unnecessary expensive screening programs.

The findings, as presented in Figure 3 and Table 1, elucidate the efficacy of the N^3 marker across various disorders. In the specific cases of AD and FTD, the N^3 marker demonstrated notable improvements in balanced accuracy scores—surpassing the second-best markers by 5.8% for AD and 7.5% for FTD. However, in alignment with the small effect sizes observed in statistical analysis, the efficacy of all markers notably declined in predicting the presence of MCI from the given variables. Here, the N^3 reached an 1.1% improvement to the next best marker, the BAG. With regard to the F1-scores, the N^3 marker achieved the highest performance in all neurodegenerative diseases, demonstrating its adeptness at balancing sensitivity and precision in detecting disease cases. While N^3's precision for MCI was 0.5% behind the normative modeling marker (NM-S) and by 5.0% in AD (NM-C), it was superior by 5.2% for FTD compared to the second best result (NM-C). Moreover, the N^3 marker displayed superior sensitivity rates in all conditions (+1.6%, +11.0% and +2.9%), highlighting its sensitivity in identifying (subtle) neurodegenerative patterns. Given the overlap to normative aging patterns and the individuality in disease manifestations, particularly in MCI, this is a notable performance increase and indicates the N^3 approach's utility in decoding sparse associations. Overall, N^3's relative superiority over other markers emphasizes its efficacy in differentiating inter-individual variability from pathological variations in unseen individuals. The results provide evidence for the expressiveness of the proposed N^3 normative modeling approach, indicating its ability to parse inter-individual heterogeneity effectively to evaluate individual measurements intricately within the broader landscape of diverse medical data.

2.3 Stability and Robustness of the N^3 marker

The calculation of the N^3 marker relies on local density estimation. As such it is highly dependent on the composition of the reference sample. Therefore, we investigate how changes to the sample composition and sample size affect the stability of the N^3 model. We retrained N^3 models with downsampled subsets of varying size, thereby mimicking smaller studies and different study participants. We then apply the different normativity models and predict normativity on an external dataset. Particularly, we evaluate if predictions remain consistent across different sample sizes and sample compositions. We quantify the stability of the normativity estimates by calculating the Intraclass Correlation Coefficient (ICC) 18 (see Methods Section 5). Results are visualized in Figure 4. We see that random samples of 200 individuals and above show consistently high stability (ICC of 0.75 and above). Moreover, the ICC converges to excellent levels (0.9 and above) in larger sample sizes, starting at 300 participants. While the results are calculated for the use case of brain structural normativity estimation, they are a first indication density-estimation based normative models can be realized by dividing larger samples into subgroups of a few hundred samples and above.

Furthermore, it is essential for normativity estimations to remain consistent and interpretable along the aging continuum, i.e., across different age groups, to avoid age biases that could complicate both research and clinical interpretations. An analysis of the age correlation of the N^3 marker (presented in Figure 4a) indicates its stability over the age range, showing no significant association to age. In comparison, traditional normative models show a significant but smaller correlation to age (ρ=0.11-0.16,

Table 1 Overview of the results achieved in statistical and machine learning analyses. To quantify the expressiveness of the different methodologial approaches, we evaluate the different biomarkers' ability in distinguishing between normative inter-individual variability and pathological alterations. We report the effect size η^2, representing the amount of variance explained by each of the different normativity markers in statistical group comparisons. We compare $\mathbf{N^3}$ - our approach, NM-S - the sum of the absolute z-scores, NM-C - the number of z-scores whose magnitude deviates beyond a threshold of ± 1.96, and the BAG - Brain Age Gap for Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), and Frontotemporal Dementia (FTD), respectively. Moreover, we report the F-statistic, reflecting the relation of the marker variance between cognitive unimpaired and diseased individuals in relation to the respective intra-group variance, further indicating its ability to identify pathology in group-level analyses. All F-statistics and effect sizes η^1 are significant ($p<0.001$). The performance results of the machine learning analyses are given, where the normativity markers are used to predict the occurrence of the neurodegenerative diseases in individual cases. The metrics provide insights into each marker's clinical utility, and overall efficacy in handling inter-individual variability and pathological variations across different neurodegenerative conditions on a single subject level. Highest performance is indicated in bold. We see that the $\mathbf{N^3}$ brain structural normativity marker shows relative superiority in relation to the other biomarkers, indicating the approach's efficacy in processing inter-individual variability and delineating potential anomalies.

Marker	F-statistic	Effect size η^2	B. Accuracy	F1-score	Sensitivity	Precision
Mild Cognitive Impairment (MCI)						
NM-C	$F(1,4565) = 74$	0.016	0.539 ± 0.010	0.385 ± 0.057	0.367 ± 0.090	0.427 ± 0.028
NM-S	$F(1,4565) = 85$	0.018	0.553 ± 0.013	0.352 ± 0.044	0.284 ± 0.070	**0.490** ± 0.044
BAG	$F(1,4565) = 220$	0.046	0.603 ± 0.011	0.516 ± 0.014	0.566 ± 0.030	0.475 ± 0.016
$\mathbf{N^3}$	$F(1,4565) =$ **326**	**0.067**	**0.614** ± 0.011	**0.529** ± 0.013	**0.582** ± 0.023	0.485 ± 0.014
Alzheimer's Disease (AD)						
NM-C	$F(1,3709) = 1{,}073$	0.225	0.733 ± 0.020	0.583 ± 0.027	0.578 ± 0.047	**0.591** ± 0.010
NM-S	$F(1,3709) = 994$	0.212	0.727 ± 0.023	0.570 ± 0.031	0.578 ± 0.057	0.567 ± 0.022
BAG	$F(1,3709) = 328$	0.081	0.676 ± 0.023	0.477 ± 0.025	0.651 ± 0.054	0.376 ± 0.014
$\mathbf{N^3}$	$F(1,3709) =$ **1,529**	**0.292**	**0.791** ± 0.020	**0.632** ± 0.020	**0.761** ± 0.049	0.541 ± 0.010
Frontotemporal Dementia (FTD)						
NM-C	$F(1,580) = 121$	0.173	0.671 ± 0.028	0.613 ± 0.043	0.499 ± 0.063	0.812 ± 0.073
NM-S	$F(1,580) = 125$	0.178	0.653 ± 0.042	0.592 ± 0.034	0.479 ± 0.047	0.790 ± 0.097
BAG	$F(1,580) = 184$	0.242	0.715 ± 0.076	0.731 ± 0.073	0.700 ± 0.073	0.765 ± 0.077
$\mathbf{N^3}$	$F(1,580) =$ **348**	**0.377**	**0.790** ± 0.063	**0.789** ± 0.059	**0.729** ± 0.063	**0.864** ± 0.080

$p<0.001$). This is a contrast to the Brain Age Gap (BAG), which exhibits a moderate age bias (ρ=0.21, $p<0.001$), even after bias correcting adjustments are made, (see Methods Section 3).

In terms of inter-marker relationships (detailed in Figure 4), the correlation analysis shows generally weak associations ($0.19 < |\rho| < 0.25$) among the various markers. Two exceptions were noted: a strong correlation (ρ=0.79) between the two normative modeling markers — expected due to their derivation from the same normative models — and a moderate to strong correlation (ρ=0.65) between the BAG and the $\mathbf{N^3}$ marker. The correlations indicate underlying differences in what these markers are measuring about brain structural normativity, suggesting a potential for a combined utility in clinical settings.

3 Discussion

We have introduced the $\mathbf{N^3}$ framework, which extends existing normative modeling approaches by accommodating a variety of normative population prototypes and evaluating individuals from multiple comparative angles. We applied it to brain structure,

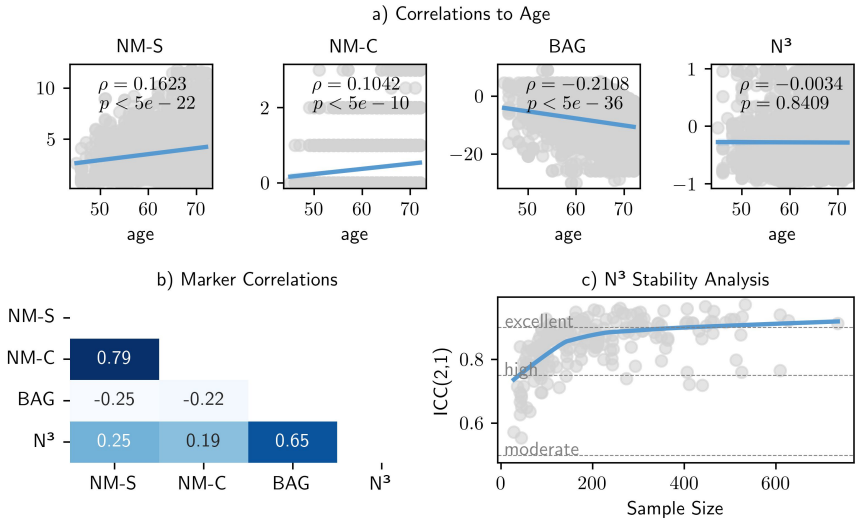

Fig. 4 Our evaluations revealed high robustness and consistency of the N³ framework. a) We explored the age bias across different brain structural biomarkers in a healthy reference sample. In contrast to the other normativity estimation approaches, the N³ marker showed no significant association to age, which allows a consistent interpretability across different age groups. b) Additionally, we calculated the correlation matrix among the different biomarkers, which emphasize the distinctiveness and complementarity of the N³ marker. c) We tested the impact of sample size and sample composition on the reliability of the N³ biomarker through intraclass correlation coefficients. To do so we repeatedly downsampled the training data to a random subset, mimicking smaller samples and different sample compositions. We see that the N³ marker exhibits high stability (ICC of 0.75 and above) starting from small sample sizes of around 100 individuals and converges to excellent stability (ICC of 0.9 and above) in sample sizes of three hundred individuals and above.

which resulted in an informative biomarker assessing aging effects from multiple perspectives along the aging continuum. Notably, the N³ framework entails several layers of context while at the same time refining individual assessments. We provided evidence that the strategic alterations of the N³ framework yield increased expressiveness and enabled superior differentiation between natural inter-individual variability and pathological alterations. In comparison to commonly used normativity scores and the widely referenced Brain Age approach, the N³ marker showed increased efficacy in identifying pathological brain structural changes.

Notably, our evaluations are based on only five variables reflecting global brain structure volumes. As such, they are broad aggregates of complex physiological features and represent the character of many clinical measurements. In our application, the N³ approach has demonstrated its ability to effectively decode the relevant information contained in these limited neurobiological variables and was able to extract meaningful insights.

Limitations of our proposed N³ framework include its reliance on larger sample sizes, a factor not always feasible in clinical studies where resource efficiency dictates

smaller study populations. To maximize statistical power and mitigate the confounding effects of clinical covariates, the heterogeneity in these smaller studies is often restricted, which inadvertently limits their generalizability and applicability of outcomes across the heterogeneous population [29, 30]. In our evaluations, the N^3 marker exhibited high stability in samples of a few hundred individuals, indicating substantial robustness in moderately-sized research study populations. Moreover, the N^3 marker showed consistency across age groups, i.e., no correlation to age, which means that its interpretation is consistent across individuals from different age groups and facilitates its interpretability in statistical analyses. Moreover, the framework's effectiveness relies on the choice of a density estimation algorithm. In our application, the Nearest Neighbor Algorithm depends on the k parameter, which defines the number of neighbors considered in the estimation of the local sample density. In our approach, limiting the number of neighbors to 10% with an upper bound to 15 prevented overly broad comparisons while maintaining sufficient robustness across all control groups. In general, the underlying algorithm can be customized for different scenarios, or adapted to accommodate different medical data modalities, e.g., by using custom distance metrics or dimensionality reduction techniques [31, 32].

We developed the N^3 approach in alignment to the goals of precision medicine. A refined definition of reference values and population norms enhances our understanding of normative variability in diverse populations and fosters the detection of individual pathological alterations [33–37]. As diversity and scale of datasets increase, we need to reevaluate how population norms are derived, applied, and interpreted in clinical practice [38–41]. The N^3 framework embraces the complexity in patient data, contextualizes it against heterogeneous population standards and parses the diversity into an interpretable and actionable metric.

The interpretation and contextualization of individual brain structures holds significant potential for various domains. As stated above, a reliable biomarker for brain structural normativity is eagerly sought in neuropsychiatric research. Here, biomarkers may enable comprehensive assessments of neurostructural alterations associated with specific symptoms, to better understand the etiology and pathogenesis of different disease phenotypes [24, 27, 42]. In general, a valid and robust neurostructural biomarker would allow us to measure the impact of environmental factors, treatment options and neuroinflammatory processes to understand disease mechanics and optimize individual disease management strategies [12, 19, 43, 44].

In the realm of neurodegenerative diseases, the ability to detect brain structural alterations early is of critical clinical relevance, as it has been shown that structural changes in the brain can manifest well before clinical symptoms become apparent [45, 46]. Furthermore, evidence supports the presence of multiple underlying neuropathological processes [17, 47], underscoring the methodological importance for models accommodating multiple disease prototypes. Here, a reliable brain structural screening tool could be attached to routine MRI scans to promote early disease interception and facilitate timely interventions that may prevent or delay disease progression [48–51]. To this end, we intend to extend our approach to process scans of different MRI tissue contrasts and evaluate different deep-learning based embeddings

to optimize information gain. Moreover, we intend to investigate the resulting marker's relation to genetic risk factors [52–55].

Our approach accommodates the multivariate nature of brain structures [56] and aligns with other modern understandings of heterogeneity, such as the concept of neurotypicality [57–59]. Traditionally seen as a uniform standard, brain architectures are now understood to encompass a spectrum of neurological function and structures, reflecting the rich diversity of the human nature. Moreover, our findings resonate with recent work by Yang et al., where the authors found a range of multiple, co-occuring patterns of brain aging [52]. Their research underscores the significant inter-individual and also intra-individual variability, underscoring the complexity and uniqueness of individual neurodegenerative processes beyond population averages.

As the critical role of individual norm deviations resonates through every facet of personalized medicine, we aim to refine and expand our normativity estimation approach to medical domains beyond brain structure. In general, the $\mathbf{N^3}$ framework aligns well with the goals of precision medicine, offering a more personalized and nuanced understanding of individual variability in aging or disease trajectories.

4 Conclusion

This approach that we call Nearest Neighbor Normativity ($\mathbf{N^3}$) interprets individual patient data in reference to a particularly matched sample, accommodates diverse population norms, and analyzes several different perspectives of normativity. Thereby, it holds significant promise for personalized healthcare. It can be applied across various medical domains to contextualize individual patient data in large and heterogeneous datasets. As we continue to refine and validate our $\mathbf{N^3}$ framework, it is our belief that the insights gained will be invaluable for shaping normativity assessments and contribute to more personalized patient care and improved clinical outcomes.

5 Methods

5.1 $\mathbf{N^3}$ algorithm

The $\mathbf{N^3}$ approach is based on local density estimation in tailored control groups. To establish a normative reference for the local density seen in a representative sample, we here use the simple and intuitive Nearest-Neighbor algorithm [25, 32].

5.1.1 Local density estimation in tailored control groups

Let $X_c \in X$ be a control group of dataset X and $C = \{c_1, c_2, \ldots, c_g\}$ be the set of g control groups, where control groups are allowed to overlap. Each control group X_c contains n samples $\{q_1, q_2, \ldots, q_n\}$, which are characterized by m features $\{a_1, a_2, \ldots, a_m\}$.

As a first step, we normalize the features in each control group c, so that their value lies in [0,1].

$$a'_{i,j} = \frac{a_{i,j} - min(\{a|a \in A_j\})}{max(\{a|a \in A_j\}) - min(\{a|a \in A_j\})}, \tag{1}$$

where $a_{i,j}$ represents feature j of the sample i in the control group X_c, and A_j are all values of feature j in the control group X_c. Each sample q_i is thus represented as a feature vector of normalized features $q_i = (a'_{i,1}, a'_{i,2}, \ldots, a'_{i,m})$. To estimate the local sample density around a particular point q_i in X_c, we define a subset $N_{q_i} \subseteq X_c$ such that it contains the k points $x' \in X_c$ which are the closest to q_i. Distance D is measured using the Euclidean distance. We define $\text{Dist}(q_i, X_c) = \{D(q, x') \mid x' \in X_c\}$ as the set of all distances from q_i to points in X_c. After sorting the points in $\text{Dist}(q_i, X_c)$ into a tuple $(d_1, d_2, \ldots, d_n)$, where $(d_1 \leq d_2 \leq \cdots \leq d_n)$, the k nearest neighbors are the first k elements.

Next, we quantify the local sample density λ of q_i as the inverse of the sum of the distance to its k nearest neighbors in control group c.

$$\lambda(q_i, c) = \frac{1}{\sum_{x' \in N_{q_i}} D(q_i, x')} \tag{2}$$

For each individual q_i in each of the control groups containing n samples, respectively, we calculate the local sample densities λ as described above .

$$\Lambda_c = \{\lambda(q_i, c) \mid i = 1, 2, \ldots, n\}, \tag{3}$$

To ensure comparability between the different control groups, we divide the local densities by the control-group specific median.

$$\lambda'(q_i, c) = \frac{\lambda(q_i, c)}{\text{median}\,(\Lambda_c)} \tag{4}$$

As a result we have a set of normalized local sample density estimations for all of the g control groups $\Lambda' = \{\Lambda'_1, \Lambda'_2, \ldots, \Lambda'_g\}$.

We introduce context to the local sample density estimations and analyze their distribution across all control groups. Due to its flexibility in accommodating various distributive shapes, we use the exponentiated Weibull distribution [60]. The distribution is fitted on all normalized local sample density estimation in Λ'. Using the fitted distribution, we derive the likelihood of a normalized local sample density estimation.

$$f(x, b, d) = bd[1 - exp(-x^d)]^{b-1} \exp(-x^d) x^{d-1}, \tag{5}$$

where $x = \lambda'(q_i, c)$ is the normalized local density value of sample q_i in control group c, b is the exponentiation parameter, and d is the shape parameter of the non-exponentiated Weibull law.

We use the fitted distribution f to convert all local sample density estimations $\lambda'(q_i, c)$ into measures of likelihood. To keep as much information as possible, we add a sign to f, which indicates in which direction a sample is deviating from the median. In this context, samples whose local sample density is smaller than the medium, receive a negative value, while samples whose local sample density is larger than the medium, have a positive value.

$$f^*(x) = \begin{cases} -f(x, b, d) & \text{if } x < 1, \\ f(x, b, d) & \text{otherwise} \end{cases} \tag{6}$$

Finally, to foster intuitive interpretation, we scale the signed likelihood f^* to an interval of [-1, 1], where -1 indicates lowest sample density found and 1 indicates maximal sample density found.

$$f^{**}(x) = 2 * \frac{f^*(x) - min(\{f^*(q|q \in X\}}{max(\{f^*(q|q \in X\}) - min(\{f^*(q|q \in X\})} - 1 \tag{7}$$

The final value f^{**} is a normativity estimation on how common the sample q_i appears within a particular control group c, measured by its local sample density λ'.

5.1.2 Normativity Profile

To create a normativity profile for an individual sample q_i, several normativity estimations in different, not mutually exclusive, control groups can be combined, evaluating the commonness of an individual measurement from multiple meaningful angles or viewpoints.

$$\phi_i = \{f^{**}(\lambda'(q_i, c_1)), f^{**}(\lambda'(q_i, c_2)), \ldots, f^{**}(\lambda'(q_i, c_g))\} \tag{8}$$

5.1.3 Meta Normativity

To synthesize the comprehensive information entailed in an individual normativity profile ϕ_i into a single, actionable metric, we conduct a second layer of normativity estimation (meta-normativity).

Basis to this is the first layer of normativity estimation, in which the local density estimation algorithm described in section 5.1.1 is applied to medical data of a population or study sample. In this step, the local sample density estimation is based on the m medical data features. Using the algorithm outputs, a normativity profile ϕ_i can be generated for each individual. The normativity profile expresses how common the medical observations are in relation to the samples contained in each control group.

In the second layer of normativity estimation, we use the normativity profile ϕ_i as input data and repeat the local sample density estimation approach. Now, the local density estimation algorithm is using the g normativity measures of ϕ as features. Thereby, we measure the commonness of a normativity profile in relation to other normativity profiles seen a particular reference population. This can either be done globally (on all normativity profiles of the sample), or again in in tailored control

groups (evaluating the commmonnness of a normativity profile with respect to a particular sample subpopulation). The output of this meta-normativity estimation is the return value of the $\mathbf{N^3}$ algorithm, what we call the $\mathbf{N^3}$ marker.

$$N^3 = f^{**}(\lambda'(\phi_i, c)) \tag{9}$$

5.1.4 Training vs. Inference Phase

The $\mathbf{N^3}$ algorithm is trained using a normative reference sample X. There are two subsequent layers of local density estimation. The first layer operates on the algorithm's input data. During the process, scaling parameters for the input features, as well as the median local sample density are derived and persisted per control group, respectively. Also, the parameters of the fitted probability density function and the final scaling function are persisted. Afterwards, all samples in X undergo the normativity evaluations and are expressed in individual normativity profiles $\Phi = \{\phi_1, \phi_2, \ldots, \phi_n\}$ (see Equation 8).

Using the resulting normativity profiles of the normative reference sample Φ as input, a second layer of normativity estimation is applied. This time, the inidivudal normativity profiles ϕ_i are subject to local sample density estimation ($\lambda'(\phi_i, c)$). Again, the scaling parameters as well as the median local sample density are persisted per control group, respectively. Control groups may now be different than those in the first stage. Finally, another probability density function is fitted, this time on the local sample densities of Φ. Again, the fitting parameters of as well as those of the scaling function are persisted.

During inference time, a novel sample p is evaluated in relation to the controls groups C of training sample X. For each control group, the feature values of p are scaled according to the parameters persisted during training, and the k nearest neighbors of p are determined, respectively. We calculate $f^{**}(\lambda'(p, c))$ in relation to samples seen in X_c. After applying the first layer of local sample density estimation, several normativity evaluations in different control groups are summarized in a normativity profile ϕ_p. In the second step, the normativity profile ϕ_p is evaluated in relation to the normativity profiles seen in the reference sample (Φ), using the parameters persisted during the second stage of training. The final output is derived by $N_p^3 = f^{**}(\lambda'(\phi_p, c))$

5.1.5 Application to Brain Structure

In our application to brain structure, we stratify the training sample by sex and age, resulting into 100 control groups containing same-aged females or males (22 to 72 years), respectively. Each sample is characterized by 5 different features, namely the brain structural volumes (GM, WM, WMH, CSF, TIV) of each individual. To mitigate different sample sizes of different age groups, we join either the lower, the upper, or both neighboring age groups of underrepresented age groups, so that the sample size per age group approximates the median sample size available per sex. We set the k parameter to 10% of the control group sample size, but limit its upper bound to 15 to prevent too broad comparisons $k = min(\text{round}(0.1 \times n), 15)$. Applying the $\mathbf{N^3}$ algorithm, we then first evaluate the commonness of an individual brain structure in comparison to all available age groups of the same sex. The result are normativity

profiles, indicating the alignment of the brain structure in relation to the reference samples seen across the aging continuum. In the next step, we use all normativity profiles (across genders) and evaluate their normativity in relation to other representative samples of the same chronological age. The final N^3 marker indicates how common a brain structural normativity profile is in the chronological age group of the individual.

5.2 Materials

Neuroimaging data from six different studies were provided by the respective consortia. Our study includes data from the German National Cohort (NAKO)[61–63], the Alzheimer's Disease Neuroimaging Initiative (ADNI) [64], the Münster-Marburg Affective Disorder Cohort (MACS) [65], the Australian Imaging, Biomarker Lifestyle Study of Aging (AIBL) [66], the Frontotemporal Lobar Degeneration Neuroimaging Initiative (NIFD), and the Open Access Series of Imaging Studies 3 (OASIS3) [67, 68]. We give a short overview of our approach to integrate these resources in our analyses, before we introduce each study population in detail below.

5.2.1 Training and Test Data

In general, if more than one measurement was available per participant, we restrict each study's dataset to the first (baseline) measurement of the participant. Exclusion criteria were applied based on age; participants younger than 22 years or older than 72 were omitted from the study, due to insufficient sample sizes in the normative reference sample. All neuroimaging data utilized in this study were T1-weighted MRI scans from these baseline measurements. These images underwent preprocessing using the standard software CAT12 (version: cjp_v0008, spm12 build v7771; cat12 build r1720) default parameters. In short, images were bias-corrected, tissue classified, and normalized to MNI-space using linear and non-linear transformations. Subsequently, the derived GM, WM, WMH, CSF, and TIV volumes were extracted.

Training Data

The training data for fitting models of the different normative modeling approaches comprised 30,047 samples from the population-based NAKO cohort (for details see below). We exclude age groups below 22 years and above 72 years due to small sample sizes ($n < 100$), which restricts the final sample to 29,883. We then fit the models of the different normative model approaches using this large and diverse sample.

Test Data

To investigate each normativity marker's effectiveness in identifying brain structural anomalies and (early) signs of neurodegeneration, additional data involving 5,857 participants were utilized, sourced from ADNI, AIBL, OASIS and NIFD datasets (for details see section 5.2.2). The collective samples include cognitively unimpaired individuals as well as those diagnosed with Mild Cognitive Impairment, Alzheimer's Disease and Frontotemporal Dementia.

Data for Stability Analysis

Finally, to evaluate the robustness of the N^3 brain structural normativity assessments, we use artificially downsampled subgroups of the NAKO study for training. Validation subsets included n=835 healthy control participants from the MACS study which predominantly comprises younger and middle-aged adults, and an additional n=1073 healthy older adults from the ADNI study to span a wider age demographic (see Methods section 5.5).

5.2.2 Study Populations

German National Cohort (NAKO)

The German National Cohort is a population-based longitudinal study initiated in 2014 aiming to investigate the risk factors for major chronic diseases in 200,000 persons living in Germany. It contains high-quality neuroimaging data from participants spanning a broad age range. In this study, we utilize the participants' 3.0-Tesla T1w-MPRAGE MRI scans (voxel size 1×1×1 mm3, repetition time/ echo time=2300/2.98, flip angle=9°) [61–63].

Alzheimer's Disease Neuroimaging Initiative (ADNI)

ADNI is a major multicenter study started in 2003, designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease. The ADNI was launched as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of neurodegeneration. We included 1.5 and 3.0-Tesla T1w-MPRAGE MRI scans adhering to the ADNI sequence protocol, for scanner specific details please see https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/mri/mri-scanner-protocols/)

Australian Imaging, Biomarker & Lifestyle Study of Aging (AIBL)

AIBL is an Australian study launched in 2006 focusing on understanding the pathways to Alzheimer's disease. The cohort includes participants diagnosed with Alzheimer's disease, mild cognitive impairment, and cognitively unimpaired elderly participants, providing insights into the aging process and the development of neurodegenerative diseases. AIBL study methodology has been reported previously [69]. MRI scans were performed using a 3D MPRAGE image (voxel size 1.2×1×1 mm3, repetition time/echo time=2300/ 2.98, flip angle=8°)[66].

NIFD Dataset

The Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI) was funded through the National Institute of Aging, and started in 2010. The primary goals of FTLDNI were to identify neuroimaging modalities and methods of analysis for tracking frontotemporal lobar degeneration (FTLD) and to assess the value of imaging versus other biomarkers in diagnostic roles. The Principal Investigator of

NIFD was Dr. Howard Rosen, MD at the University of California, San Francisco. We use the provided 3D MPRAGE T1-weighted images (voxel size 1×1×1 mm3, repetition time/echo time=2300/2.9, matrix = 240 × 256 × 160) The data are the result of collaborative efforts at three sites in North America. For up-to-date information on participation and protocol, please visit http://memory.ucsf.edu/research/studies/nifd

Open Access Series of Imaging Studies 3 (OASIS3)

OASIS3 serves as a comprehensive digital repository for MRI brain data that supports longitudinal studies of normal aging and cognitive decline [67, 68]. The project is distinguished by its wide age range of participants, providing diverse datasets that enhance the understanding of late-life brain diseases alongside physiological aging processes. We include 3D MPRAGE T1-weighted images (voxel size 1.0 or 1.2×1×1 mm3, repetition time/echo time=2300/2.95 or 2400/3.16 (depending on the scanner), flip angle=9°, FoV=240 or 256mm)

Marburg-Münster Affective Disorder Cohort Study (MACS)

The MACS cohort is part of the DFG-funded research group FOR2107 cohort, researching the etiology and progression of affective disorders [65]. The goal is to integrate and understand the clinical and neurobiological effects of genetisc and environmental factors, and their complex interactions. Participants received financial compensation and gave written informed consent. We use the T1-weighted neuroimaging scans of n=835 healthy control participants to evaluate stability of the N^3 models. Images were in Marburg (MR) or Münster (MS) (voxel size 1×1×1 mm3, repetition time/echo time=MR: 1900, MS: 2130/MR: 2.26, MS: 2.28, flip angle=8°, FoV = 256 mm, matrix = 256 × 256, slice thickness = 1 mm)

Table 2 Study Data Summary

Study	Group	N Included	Mean Age	Sex
ADNI	HC	1073	68.36 ± 3.3	634 females (59.09%)
	MCI	1529	66.71 ± 4.25	729 females (47.67%)
	AD	588	67.2 ± 4.65	291 females (49.48%)
AIBL	HC	368	68.00 ± 2.77	217 females (58.97%)
	MCI	78	68.05 ± 3.54	33 females (42.31%)
	AD	28	66.89 ± 4.44	16 females (57.14%)
OASIS3	HC	1643	63.36 ± 6.85	1028 females (62.57%)
	MCI	63	66.67 ± 4.85	37 females (58.73%)
	AD	228	66.54 ± 4.94	97 females (42.54%)
NIFD	HC	263	62.71 ± 6.41	148 females (56.27%)
	FTD	317	63.26 ± 5.66	120 females (37.85%)
MACS	HC	835	35.71 ± 12.6	528 females (63.23%)
NAKO	HC	29883	48.45 ± 12.09	13201 females (44.18%)

5.3 Brain Age Model

In the Brain Age paradigm, the brain structure is evaluated with respect to aging effects seen in a healthy reference sample. This is realized by means of a machine

learning model trained to predict chronological age from brain structure. The deviation between chronological and predicted age is referred to as the Brain Age Gap (BAG). While a small BAG is considered normative and age-appropriate, a larger positive or negative BAG symbolizes premature or delayed neurostructural degeneration, respectively. The resulting normativity estimation, i.e. the BAG values, have been associated with numerous neurological and psychiatric conditions [11, 12]. For comparison with N^3, we train a Brain Age Model using the Python library photonai [70]. We use 90% of the available normative dataset for model training. We use a Support Vector Machine (SVM), for which we optimize the C and gamma parameters in the nested-cross-validation procedure (k=10 outer folds and two randomly shuffled inner folds with a test size of 0.1). The best model achieves an average MAE of 5.43. Finally, we use the remaining 10% of the normative training data to train a linear age bias correction as described in Peng et al. [71]. For the evaluation of unseen samples, we use the Brain Age SVM model to predict age and apply the age correction model, before we calculate the difference between the chronological and predicted age, the BAG.

5.4 Normative Modeling

We calculate normative models on the training data using the Predictive Clinical Neuroscience toolkit as described in Rutherford et al. [22]. To train the models, we normalize GM, WM, WMH, CSF by Total Intracranial Volume (TIV) and fit Bayesian Linear Regression models with default parameters. Subsequently, z-scores for each of the variables are derived, which we aggregate into two normative modeling markers: one being the sum of the absolute z-scores, the second counting the number of absolute z-scores > 1.96.

5.5 Statistical Analysis

A Type III Sum of Squares ANOVA was performed using an ordinary least squares (OLS) model to assess the discriminative and explanatory power of each normativity marker in distinguishing patients from controls. The model was adjusted for potential confounders, including age, age squared (to mitigate non-linear effects), sex and scanner. Partial eta squared (η^2) was used to quantify effect size, providing an estimate of how much variance in disease progression could be explained by each normativity marker, alongside a 95% confidence interval.

We evaluate and rank the different normativity markers by post-hoc comparisons of their effect size. To test the observed marker differences for statistical significance, we calculate the ANOVA for each marker with 1000 random permutations. To determine the p value of the marker differences, we evaluate the actual difference between the η^2 of our marker N^3 and the η^2 another marker, with those found in the 1000 random permutations.

To assess each normativity marker's consistency across age groups, an analysis of age bias was conducted using Spearman's rank correlation to evaluate the correlation between the normativity estimation values and age in healthy controls.

To assess stability of the N^3 models, the Intraclass Correlation Coefficient (ICC) model (2,1) was applied. For this purpose, we used the NAKO sample to train the

normativity models, which were downsampled to mimic smaller study populations. Particularly, we divide the training set in k=[10, 5, 3, 2] non-overlapping parts of equal size, train normativity models within each of these subsets, and use external test data to ensure the stability of the normativity estimates. The stability of the normativity estimates was tested using data from the ADNI and MACS cohort, (see Methods section 5.2.1). To ensure validity of the test, we use only age groups with more than 500 samples available from the training sample and more than 20 samples in the test samples.

All statistical analyses were implemented in Python using the *scipy, statsmodels* and pingouin libraries.

5.6 Machine Learning Analysis

The effectiveness of aging markers in classifying neurodegenerative diseases was further explored through machine learning techniques. We assessed various performance metrics including balanced accuracy, recall, precision, and F1-score. Our analytical pipeline employed the open-source Python framework photonai [70]. The analysis involved nested cross-validation to robustly estimate model performance and avoid overfitting, using k=5 outer folds and k=10 inner folds, each fold stratified to entail a balanced proportion of samples from the diseased class. Hyperparameter optimization was performed via Grid Search to fine-tune the support vector machine (SVM) parameters C and gamma. The machine learning pipeline included steps for z-normalization and balanced sampling (random under-sampling techniques) to address class imbalance within the training data. We measure balanced accuracy, recall, precision and f1 score of each of the normativity markers in the classification of neurodegenerative diseases.

Supplementary information.

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Declarations

Data Availability

Data were obtained from the German National Cohort (NAKO), the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Open Access Series of Imaging Studies

3 (OASIS3), the Frontotemporal Lobar Degeneration Neuroimaging Initiative (NIFD, and the Australian Imaging, Biomarker Lifestyle Study of Aging (AIBL). Data of the MACS study are not publicly available. All other data are available upon request via the access management systems of the respective studies. (NAKO: nako.de/forschung, ADNI, AIBL, NIFD: ida.loni.usc.edu, OASIS3: sites.wustl.edu/oasisbrains)

Code Availability

Code to realize the normativity estimation calculations within the $\mathbf{N^3}$ framework is written in the Python programming language and is provided as an open-source resource to the scientific community on Github (link tbd).

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