Research Article

Hippocampal atrophy subtypes of Alzheimer's disease using automatic MRI in a memory clinic cohort – clinical implications

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Short Title: Subtypes of Alzheimer's disease as evaluated by atrophy of the hippocampus on MRI

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Abstract

Introduction: One pathological hallmark of Alzheimer's disease (AD) is atrophy of medial temporal brain regions that can be visualized on MRI, but not all patients will have atrophy. The aim was to use MRI to categorize patients according to their hippocampal atrophy status and to present prevalence of the subtypes, difference in clinical symptomatology and progression, and factors associated with hippocampal subtypes.

Methods: We included 215 patients with AD who had been assessed with the clinically available MRI software NeuroQuant (NQ, CorTechs labs/University of California, San Diego, CA, USA). NQ measures the hippocampus volume and calculates a normative percentile. Atrophy was regarded present if the percentile was ≤5. Demographics, cognitive measurements, AD phenotypes, *APOE* status, and results from cerebrospinal fluid and amyloid PET analyses were included as explanatory variables of the hippocampal subtypes.

Results: Of all, 60% had no hippocampal atrophy. These patients were younger and less cognitively impaired concerning global measures, memory function and abstraction, but as impaired concerning executive, visuospatial and semantic fluency, and more of them had non-amnestic AD, compared to those with hippocampal atrophy. No difference in progression rate was observed between the two groups. In MCI patients, amyloid pathology was associated with the no hippocampal atrophy group.

Discussion/Conclusion: The results have clinical implications. Clinicians should be aware of the large proportion of AD patients presenting without atrophy of the hippocampus as measured with this clinical MRI method in the diagnostic set up and that non-amnestic phenotypes are more common in this group as compared to those with atrophy. Further, the findings are relevant in clinical trials.

Introduction

Alzheimer's disease (AD) is the major cause of dementia affecting an increasing amount of people globally. A recent Norwegian population study found that 101.000 persons (1.88%) have dementia, of whom almost 60% have AD [1]. AD neuropathology is characterized by amyloid plaques extracellularly in the brain, intracellular tangles of phosphorylated tau (p-tau) protein, and inflammatory changes. According to the Braak staging of neuropathological changes, tangles appear first in the medial temporal regions (the transentorhinal cortex and hippocampus) and in the later stages (V-VI) also in neocortical regions [2]. However, during recent years, there has been an increasing focus on identifying AD subtypes showing atypical distribution of tangle pathology. Murray et al. demonstrated that in about 11% of AD patients the neurofibrillary tangle density was lower in the hippocampal region as compared to cortical regions (hippocampal sparing AD) whereas in 14% tangles predominated in the hippocampal region (limbic predominant AD), and the remaining 75% were classified as typical AD, presenting tangles of equal density in both cortical and hippocampal regions [3]. As tangle density and atrophy visualized with magnetic resonance imaging (MRI) have been found to correlate [4], several studies have used MRI as a surrogate marker of regional tau pathology and found almost identical subtypes as Murray et al. reported including an additional subtype characterized by minimal atrophy in both cortical and hippocampal regions [5-10]. Further, atrophy subtypes have been found to correlate with clinical symptom profiles: The limbic predominant and typical atrophy subtypes presenting with amnestic symptoms, whereas the hippocampal sparing subtype has shown more non-amnestic symptoms such as executive, language, or visuospatial deficits [5, 9]. Findings on clinical progression rate of the various subtypes have been inconsistent. Some studies reported a faster progression in typical and hippocampal sparing AD [3, 6, 11], others have found faster progression in typical and limbic predominant types [7, 12], while our group did not find any difference in progression rate in a previous study [8].
The focus on AD subtypes is important as differences in clinical symptomatology, progression rate, regional vulnerability and possibly underlying neurobiology could have major impact on both clinical work-up and follow-up and in treatment trials [13].

In a recent study, Vogel et al. measuring regional tau positron emission tomography (PET) found four subtypes of AD, similar to those previously described [13]. While post-mortem examination and PET are the more accurate ways to classify patients based on tau pathology, MRI is the more widely available method. Previous MRI studies have used either MRI methods intended only for research or visual rating methods that are dependent on experienced personnel. At Oslo University Hospital (OUH), a clinically feasible automatic MRI software, NeuroQuant® (NQ), has been in use as a clinical

tool to rapidly evaluate atrophy. We compared the NQ measure of hippocampus volume with the well-known visual assessment scale of Scheltens et al. [14] previously and found high correlations between the methods and a slight advantage to NQ in discriminating dementia from non-dementia patients [15]. Thus, in the present study we used NQ to subtype clinically diagnosed AD patients according to their hippocampal atrophy status. We hypothesized that most of the patients with clinical AD would have hippocampal atrophy. We further hypothesized that patients with and without hippocampal atrophy would differ in clinical symptomatology and symptom profiles i.e. phenotypes, and in clinical progression rate. Lastly, we wanted to examine which characteristics were associated with the two hippocampal atrophy subtypes . We also wanted to test these hypotheses in a subset of amyloid positive patients.

Materials and Methods

Participants

The patients were recruited from the memory clinic at OUH between January 2010 and August 2020. Patients referred to this clinic are asked to participate in a national quality and research register (The Norwegian registry of persons assessed for cognitive symptoms, NorCog). About 80% of all referred patients are included into the register (personal communication with the register). Of 2,305 patients recruited into the register during the inclusion period, 625 were examined with MRI of the brain at the department of radiology at OUH at their first visit to the clinic, or during follow-up, as part of the clinical diagnostic work-up. For the present study, only patients fulfilling the clinical criteria of probable AD at the mild cognitive impairment (MCI) or dementia stages were included (diagnostic criteria, see below). A total of 215 patients fulfilled these criteria, of whom 135 had a clinical follow-up assessment on average 31 months (SD 17, range six to 100 months) after baseline.

Diagnoses and clinical assessments

Patients included in NorCog are assessed with a comprehensive standardized examination protocol [16]. The patients were re-evaluated post hoc in 2018-2019 by one of two experienced physicians (KP or THE) using all available data from the clinical records both at the time of MRI (+/- 6 months) and at the patient's last clinical assessment. Diagnoses were made and the Clinical Dementia Rating scale-sum of boxes (CDR-SB) was scored. The DSM-5 criteria were used to diagnose dementia [17] and the National Institute on Aging and the Alzheimer's Association (NIA/AA) 2011 criteria were used to diagnose dementia due to probable AD [18]. To diagnose MCI, the NIA/AA 2011 MCI-core

clinical criteria were used [19]. In addition, the MCI patients had to have had a gradual disease onset, in line with the dementia due to AD patients, to increase the likelihood that they had MCI due to AD. All patients were further subdivided into amnestic and non-amnestic phenotypes, and the non-amnestic phenotype was further divided into a language, a visuospatial, and a dysexecutive/frontal phenotype [18]. Results on atrophy from the MRI examination were not included in the diagnostic process or in the evaluation of CDR.

The CDR is a global measure of cognitive and functional impairment, including six items. Each item is scored from zero to 3, the higher the score the greater the impairment. The items can be summed up as a continuous variable "CDR sum of boxes" (CDR-SB) ranging from zero to 18 [20]. The annual CDR-SB change was calculated by dividing the difference between CDR-SB at follow-up and baseline with the follow-up time (in years) and used as a measure of disease progression. Both CDR raters were CDR certified.

The following tests from NorCog were included: The Norwegian version of the Mini Mental State Examination (MMSE-NR) that gives a score from zero to 30, the higher score the better global cognitive capacity [21, 22]; The Clock drawing test (CDT), measuring visuoconstructive and executive capacity from zero to 5, the higher score the better cognitive capacity [23]; The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word delayed recall test, with scores from zero to 10, the higher score the better the learning and retrieving capacity [24]; The Trail Making test B, measured in seconds to complete the test, the longer the time, the poorer the psychomotor speed and executive function [25]; Figure copying from the CERAD constructional praxis exercise, with scores from zero to 11, the higher score the better the visuoconstruction ability [24]; The Boston naming test-short version, from zero to 15, the higher score the better word retrieval [26]; The Controlled oral word association test (COWAT-FAS), the higher the produced number of words, the better the phonemic fluency, executive function and motor speed [27]; The Animal naming test, the higher the number of produced words the better the semantic fluency [28]; and finally, similarities from The Neurobehavioral Cognitive Status Examination (COGNISTAT) from zero to 8, the higher the score the better the capacity in abstractive skills [29].

MRI assessment

All MRI examinations were carried out at the same MRI lab using a GE Signa HDxt 3T scanner that was upgraded with new hardware in 2015 (GE Discovery MR750) and 2019 (GE Signa Premier). The scans were assessed with the clinically available software NeuroQuant® (NQ, CorTechs labs/University of California, San Diego, CA, USA), version one and two. NQ produces an automatic

volumetric report of several brain regions. The method has proved to be valid against gold standard measures (manual segmentation) and with reliable reproducibility [30]. Through comparisons with a normative dataset of healthy controls between 0-100 years, a percentile adjusting for age, sex, and head size, of selective regions, e.g. the hippocampus [31] is calculated. Generally, a cut-off of 1.65 SD or more from a mean is regarded as abnormal [32]. Thus, patients were categorized as having hippocampal atrophy if the percentile of the sum of the right and left hippocampi was ≤-1.65 SD i.e ≤the 5^{th} percentile. If above the 5^{th} percentile, the patient was categorized as the no hippocampal atrophy subtype.

Other assessments

Apolipoprotein E (*APOE*) genotyping was done in 143 patients by deCODE Genetics, Reykjavik, Iceland using the Illumina Infinium OmniExpress v1.1 chip. The result was dichotomized based on whether the patient carried at least one *APOE-ε4* allele, or not.

Cerebrospinal fluid (CSF) biomarkers of amyloid-β-42 (Aβ), total tau (t-tau) and phosphorylated tau 181 (p-tau) were analyzed at Akershus University Hospital (AHUS) using ELISA technique with the Innotest kit (Innogenetics, Ghent, Belgium). Due to changes in analyzing methods, cut-offs have been changed during the inclusion period of this study and results were therefor dichotomized as "pathological" and "non-pathological" according to the applicable cut-offs. ^{18}F-Flutemetamol PET (amyloid PET) was carried out at the Department of Nuclear Medicine at OUH. CSF results and amyloid PET results were included in the study only in patients who had a pathological result any time prior to, or maximum 12 months after the MRI examination, or who had a non-pathological result maximum 12 months prior to or any time after the MRI examination. Thus, the Aβ status was available in 138 patients (109 CSF, 29 PET) and the p-tau and t-tau statuses were available in 107 patients.

Statistical analyses

The data was analyzed using IBM SPSS Statistics for Windows, version 27, Armonk, NY, USA. Independent samples t-test for continuous variables and χ^2-test for categorical variables were applied to compare groups (table 1 and 2). Level of significance was set at p 0.05. Further, adjusted logistic regression analyses were performed for each clinical explanatory variable, with hippocampal subtype as the outcome variable, adjusting for several covariates: age, sex, years of education, clinical stage (MCI/dementia), MRI scanner update (three dummy variables), and NQ version (1 or 2), from now on referred to as "basic covariates" (column 5 of table 2).

Logistic regression analyses were also performed to explore associations to hippocampal subtypes adding explanatory variables in separate models, adjusting also for basic covariates. First, clinically relevant and available measures were included in two separate models (amnestic type in the first model, and MMSE as a continuous measure of disease stage added in the second model) (table 3). Secondly, in the subgroup of patients that had relevant AD biomarkers available, i.e. amyloid and *APOE* status, two further models were set up (*APOE* status in the first model, and amyloid pathology added in the second model) (table 4). In the logistic regression analyses the Nagelkerke R^2 is presented as a measure of the explained variance.

Results

Patient characteristics

Of the 215 patients with probable AD, 152 had dementia and 63 had MCI. Patient characteristics are presented in table 1. Compared to dementia patients, the MCI patients had more years of education, better cognitive function, higher mean hippocampus percentile, and more of the MCI patients belonged to the no hippocampal atrophy subtype. Of patients with available CSF/amyloid PET, and/or *APOE* status, 104 (75%) had amyloid pathology, 53 (50%) p-tau pathology, 70 (65%) t-tau pathology, and 101 (71%) were *APOE-ε4* carriers. A higher proportion of patients with dementia had amyloid, p-tau, and t-tau pathology, while no difference in *APOE-ε4* carriers was observed between the two disease stages.

No hippocampal atrophy vs. hippocampal atrophy subtypes

Table 2 presents patient characteristics by hippocampal subtype, and unadjusted and adjusted group comparison results (column 4 and 5). A total of 128 (60%) had no hippocampal atrophy (48 (76%) of MCI and 80 (53%) of dementia patients). The no hippocampal atrophy patients were younger and had better cognitive function in several domains. Adjusted for basic covariates they had better MMSE, CDR-SB, memory function, and abstraction scores, whereas no differences in executive, visuospatial, semantic fluency, or word retrieval functions were observed between the two hippocampal subtypes. The amnestic phenotype was more prevalent in patients with hippocampal atrophy, while the logopenic and executive phenotypes were more prevalent in those who had no hippocampal atrophy. In adjusted analysis, the amnestic variant was still associated with the hippocampal atrophy subtype (p 0.013). Adjusted analysis of each non-amnestic phenotype was not applicable due to low numbers.

Progression rate as measured by the annual CDR-SB change did not differ between the two

hippocampal subtypes, neither unadjusted nor adjusted for basic covariates and follow-up time. Subanalyses of MCI and dementia patients separately showed that in patients with dementia, amyloid pathology did not differ between the two hippocampal subtypes (45 (83%) vs 39 (87%), p 0.645). In MCI however, 18 (62%) of the no hippocampal atrophy patients had amyloid pathology as compared to 2 (20%) of those with hippocampal atrophy (p 0.022).

Analyses including only patients with amyloid pathology

In subanalyses of 104 patients with amyloid pathology (supplemental table 1), 61% had no hippocampal atrophy (90% of MCI and 54% of dementia patients, p 0.003). Comparisons between the two hippocampal subtypes gave similar results regarding demography and most cognitive measures as for the whole sample, but no difference in amnestic phenotype prevalence was found (88% in hippocampal atrophy and 79% in no hippocampal atrophy, p 0.266). However, more of the patients with hippocampal atrophy were *APOE-ε4* positive (96% vs 67%, p 0.007).
In these patients with amyloid pathology, 58% had pathological p-tau levels, and 76% had pathological t-tau levels, and there was no difference in amount of patients with pathological p-tau or t-tau levels between the two hippocampal subtypes (p 0.526 and p 0.825, respectively).

Associations to hippocampal subtypes

Stepwise logistic regression analyses are presented in tables 3 (all patients, without missing values) and 4 (patients with available amyloid and *APOE* status, without missing values). Having the non-amnestic phenotype and having a higher MMSE were associated with the no hippocampal atrophy subtype (table 3). In patients with amyloid and *APOE* status available (a substantially lower n, table 4), younger age, male sex, non-amnestic phenotype, a higher MMSE, and being amyloid positive were associated with the no hippocampal atrophy subtype (table 4). Adding these biomarkers increased the Nagelkerke R^2 from 0.23 to 0.44.

Reanalysis using the 10th percentile as the cutoff for hippocampal atrophy increased the hippocampal atrophy group to 50% of the cohort but did not change the main results.

Discussion/Conclusion

We found that 60% of the patients lacked atrophy of the hippocampi when using an age and sex adjusted five percentile hippocampal volume as the cutoff for normality. The no hippocampal atrophy patients were younger; they were less cognitively impaired concerning global measures, memory function and abstraction, but as impaired concerning executive, visuospatial and semantic

fluency, and more had non-amnestic phenotypes, compared to patients with hippocampal atrophy. No difference in progression rate was observed. *APOE-ε4* positivity was associated with hippocampal atrophy in amyloid positive patients. Surprisingly, in MCI patients, amyloid pathology was associated with the no hippocampal atrophy subtype.

Prevalence of the no hippocampal atrophy and hippocampal atrophy subtypes

A surprisingly high proportion had no hippocampal atrophy regardless of amyloid pathology. In the MCI group, this finding is not unexpected, as these patients are at an earlier disease stage and may not yet have developed overt neurodegeneration and subsequent atrophy. In the dementia group the high proportion of patients without atrophy was unexpected as it is expected that neurodegeneration of hippocampi should have taken place at a stage of AD when symptoms of dementia are present.

Comparison with previous work on AD atrophy subtypes is not straightforward as information on cortical atrophy lacked in the present study but has been incorporated into the subtyping methods in previous studies. Thus, our no hippocampal atrophy subtype includes both hippocampal sparing (demands cortical atrophy) and minimal atrophy (minimal atrophy in both medial temporal and cortical areas) subtypes as defined by previous studies [7]. Ekman et al. found that 61% of non-progressing, and 41% of progressing MCI patients [33] belonged to hippocampal sparing or minimal atrophy subtypes, while a meta-analysis by Ferreira et al. [9] including AD patients at the dementia stage reported that proportion to be 32%. The figures varied substantially between studies included in the meta-analysis, possibly due to different subtyping algorithms and modalities and different characteristics of patients such as age and educational level [9]. Nevertheless, these previously reported results are lower than our findings of 76% of the MCI and 53% of the dementia patients belonging to the no hippocampal atrophy subtype. Both the inclusion of younger patients and non-amnestic patients in our study may explain a higher prevalence of no hippocampal atrophy patients, as non-amnestic patients were excluded in many other studies [9]. Educational level did not substantially differ between our hippocampal subtypes.
In patients with amyloid pathology the no hippocampal atrophy subtype was found as prevalent as in the whole sample. In MCI, the proportion of patients having amyloid pathology was higher in the no hippocampal atrophy group as compared to in the hippocampal atrophy group. Thus, the inclusion of amyloid negative patients in the present study does not seem to explain a high prevalence of the no hippocampal atrophy subtype.

Clinical differences, phenotypes, and progression rate

Patients with hippocampal atrophy had poorer results for memory function and abstraction, as well as lower MMSE and higher CDR-SB scores. Both MMSE and CDR-SB involve several items on memory and orientation, functions correlated to medial temporal lobe structures, especially the hippocampus [34, 35]. On the other side, symptoms related to neocortical regions like executive, visuospatial, and word retrieval functions, were equally impaired in both subtypes. The reason for abstraction being poorer in patients with hippocampal atrophy is less straightforward to explain, as abstraction function is assumed to be connected to the prefrontal cortex and would thus be expected to be as impaired in both subtypes [36]. Further, more of the no hippocampal atrophy patients had a non-amnestic phenotype. This is in line with results of previous studies. Petersen et al. showed that regional neurofibrillary tangle burden correlated with clinical variants where cortical burden was associated with non-amnestic presentations and hippocampal burden was associated with memory deficits and an amnestic phenotype [37]. In our patients with amyloid pathology there was no association between phenotype and hippocampal subtype, but the numbers of patients included in this subanalysis was substantially smaller (n=215 vs n=104).

We did not find any differences in progression rate between the hippocampal subtypes. Previous studies have found conflicting results concerning progression rate in atrophy subtypes [3, 6-8, 11, 12]. As we do not know the cortical atrophy component in the patients in the present study, and cortical atrophy has been found to be the driver of progression rate, conclusions are hard to make based on our data [11].

Factors associated with hippocampal subtypes

From the regression analysis with clinically available data, having a non-amnestic phenotype and a higher MMSE score were associated to the no hippocampal atrophy subtype. Including amyloid and *APOE* status to the models, the Nagelkerke R^2 increased from 0.23 to 0.44. In addition to having a higher MMSE score and a non-amnestic phenotype, lower age, in line with a previous study [9], being male, and having amyloid pathology were associated to the no hippocampal atrophy subtype. The last association was unexpected and was partly driven by the fact that in MCI, more patients in the no hippocampal atrophy group had amyloid pathology as compared to in the hippocampal atrophy group. We assume that MCI patients in the AD continuum have not yet developed hippocampal atrophy, despite having amyloid pathology. This is in line with the amyloid cascade hypothesis saying that deposition of beta-amyloid in the brain is the first pathophysiological event in AD [38]. On the other hand, we suggest that the MCI patients without amyloid pathology, with hippocampal atrophy (n 8), might suffer from another underlying neuropathology, e.g. suspected

non-Alzheimer pathology (SNAP) including primary age related tauopathy (PART), cerebrovascular disease, hippocampal sclerosis, or other causes of neurodegeneration [39].

The presence of the *APOE-ε4* allele was associated with the hippocampal atrophy subtype in amyloid positive patients but did not explain hippocampal atrophy status in adjusted regression analyses of the complete cohort of both amyloid positive and negative patients. A positive association between *APOE-ε4* carriers and hippocampal atrophy subtypes has been found in previous studies as well [9, 10]. In the review by Ferreira et al., *APOE-ε4* positivity and its role in hippocampal vulnerability is interestingly pointed to, at the same time describing findings of *APOE-ε4* negativity being associated to posterior brain involvement. Different risk factors like *APOE-ε4* positivity, protective factors, and concomitant non-AD pathology and the coexistence and associations between these are discussed as possible explanations of regional vulnerability patterns in several studies [9, 10] .

Limitations

One limitation of the present study is the lack of information on cortical atrophy, which made it difficult to compare our results with previous studies. However, the purpose of the present study was to examine subtypes based on hippocampal atrophy status only, as this is currently the most used MRI marker in the clinical work-up of AD. Another limitation is that we do not know what the best percentile cutoff is to determine a pathological hippocampal volume. The present study is the first using NQ percentiles in this setting. The percentile output of the NQ report is calculated based on total hippocampi volume of both hemispheres. Due to this, patients with unilateral atrophy will probably yield a percentile above 5 and the test therefore loses sensitivity but gains a higher specificity. Also, considering the low prevalence of hippocampal atrophy, it might be that our selected 5^{th} percentile cutoff was too conservative. However, using the 10th percentile as the cutoff did not change the main results, and only increased the hippocampal atrophy group to 50% of the cohort. On the other hand, the 5^{th} percentile, or even the 2. percentile, are common cutoffs that clinicians use when evaluating patients. A third limitation is the fact that amyloid status was not available in all patients and that for those with available status, 49% of MCI and 15% of dementia were amyloid negative, questioning the diagnostic method. Several factors have been found to influence the validity of amyloid markers on the one side, e.g age [40], but on the other side we believe different SNAP pathologies might also explain amyloid negative results [39]. Nevertheless, we intended to use well-known clinical criteria, not incorporating biomarkers for the main aims of the study to make it clinically naturalistic. Similarly, clinically commonly appearing heterogeneity in MRI hardware and NQ software might introduce bias but was adjusted for in regression analyses.

Finally, a strength of the study is that we included AD patients at both MCI and dementia stages as the shift from MCI to dementia is arbitrary, while most previous subtyping studies have included only one disease stage.

In conclusion, patients fulfilling clinical criteria for AD but lacking hippocampal atrophy are common, even among patients with amyloid pathology, and non-amnestic phenotypes are overrepresented in these patients. This knowledge has implications for clinicians in the diagnostic work-up of AD. Progression rate did not differ between groups. Patients with MCI were overrepresented in the no hippocampal atrophy group, being at an earlier disease stage. *APOE-ε4* carrier status was associated with hippocampal atrophy in amyloid positive patients.

Statements

Acknowledgement

We want to acknowledge the Norwegian registry of persons assessed for cognitive symptoms (NorCog), for providing access to patient data.

Statement of Ethics

All patients gave written informed consent to be included in NorCog. Patients included in the NorCog registry give their consent that all information collected at their evaluations at the clinic, including all data collected during follow-up, can be included in the register and used for research. Only patients with the capacity to consent are included in NorCog.

The present study has been approved by the Regional Committee of Medical Research Ethics of the South-East Norway (REC South-East number 2019/79) and includes the use of data from both NorCog and MRI data.

Conflict of Interest Statement

KP was a rater for drug trials with Roche BN29553 in 2018, and with NovoNordisk NN6534-4730 in 2021, outside of the submitted work.

KE and GGT have nothing to declare

GS has received honoraria for a lecture on a meeting sponsored by Biogen and participated in an advisory board meeting for Biogen.

ABK has been/is principal investigator for the drug trials Boehringer-Ingelheim (1346.0023), Roche (BN29553), and Novo Nordisk (NN6535-4730).

THE was a rater for the drug trials Boehringer-Ingelheim (1346.0023) and Roche (BN29553), outside of the submitted work.

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Author Contributions

KP and KE designed the study in collaboration with all authors at various steps. KP, THE, ABK and GS collected and cleaned the data. KP performed the analyses. KP and KE interpreted the analyses. KP drafted the manuscript. All authors collaboratively revised the manuscript and approved its final version.

Data Availability Statement

The data that support the results and conclusion of this study are, due to data protection regulations, available upon request to the corresponding author.

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Legend of figures: Figure 1. The NeuroQuant report.