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Volume and shape of subcortical grey matter structures related to headache: a population-based imaging study in the Nord-Trøndelag Health Study

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Abstract

Background: The relationship between subcortical nuclei and headache is unclear. Most previous studies were conducted in small clinical migraine samples. In the present population-based MRI study, we hypothesized that headache sufferers exhibit reduced volume and deformation of the nucleus accumbens compared to non-sufferers.

Methods: 1006 participants (50-66 years) from the third Nord-Trøndelag Health Survey, were randomly selected to undergo a brain MRI at 1.5 T. Volume and shape of the subcortical nuclei (accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus) from T1 weighted 3D scans were obtained in FreeSurfer and FSL. The association with nine different questionnaire-based headache categories (e.g. migraine, tension-type headache) was evaluated using analysis of covariance corrected for age, sex, intracranial volume, blood pressure and alcohol consumption.

Results: No effect of headache status on accumbens volume and shape was present, but small differences in volume of putamen and caudate, and in bilateral putaminal shape were found. A post hoc analysis showed that the larger caudate volume was strongly associated with increasing white matter hyperintensities.

Conclusion: This population-based study did not confirm our hypothesis that headache sufferers have smaller volume and different shape of the accumbens compared to non-sufferers. In exploratory analyses only small differences in volume and shape of subcortical nuclei between headache sufferers and non-sufferers were found.

Keywords: Neuroimaging, Surface-based methods, General population, HUNT

Background

Headache is among the most prevalent disorders worldwide and a major cause of years lived with disability(1). Almost 50% of the population report suffering from headache the past year, making it among the most frequent complaints seen in general practice(2). One of the most disabling types of headache, migraine, was formerly believed to mostly be a vascular disease, but newer evidence points to a considerable neuronal component in the pathophysiology(3). Thus, much is still unclear regarding the etiology and pathophysiology of headache and its subtypes, and it is of great interest to investigate the brain's morphology among those suffering from headache.

The majority of the structural imaging studies of people with headache have investigated the brain's cortex in migraineurs. A few studies have looked at subcortical grey matter and headache, and then mostly in small clinic-based migraine samples. These studies have reported somewhat inconsistent findings with reduced volume of the nucleus accumbens(4), hippocampus(5, 6) and of different subnuclei of the thalamus(7), both increased and decreased volume of the caudate(4, 8) and increased volume of the putamen(9). Further, the shape of thalamus, striatum and pallidum was reported to be similar in the only study of subcortical shape differences between a migraine and control group(7).

In chronic pain conditions, sharing clinical characteristics with headache, meta-analyses have revealed somewhat similar results with altered structure of the putamen, thalamus and accumbens(10-12). Lately, increasing attention has been given to the nucleus accumbens as an important modulator of pain(12, 13). One study recently found chronic pain patients to have a reduction in reward responsiveness and volume of the accumbens(14). Furthermore a PET scan of a 36 year-old female with migraine showed reductions in μ-opioid receptor availability in the accumbens during the ictal phase(15).

The aim of the present population-based study was to investigate the association between headache (migraine and tension-type headache (TTH) included) and the volume and shape of the main subcortical grey matter structures (accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus). Based on previous knowledge we hypothesized that headache sufferers, regardless of subtype, would exhibit structural difference of the nucleus accumbens, i.e. smaller volume and difference in shape, compared to those not suffering from headache. In addition to testing this hypothesis, similar exploratory analyses were performed for the other subcortical nuclei.

Material and methods

Ethical approval

This study was approved by the Regional Committee for ethics in Medical Research. The HUNT study was in addition approved by the Norwegian Data Inspectorate. All participants gave their informed, written consent.

The HUNT Cohort

Participants were recruited from the Nord-Trøndelag Health Surveys (HUNT), which is a general population survey of the entire population aged ≥ 20 years in Nord-Trøndelag County, Norway. Surveys collecting a wide range health related data from questionnaires and other investigations (e.g. blood samples, blood pressure) were conducted in 1984-1986 (HUNT1), 1995-1997 (HUNT2) and 2006-2008 (HUNT3).

As part of HUNT3 a group of 1006 individuals (530 women), all between 50 and 65 years at the time of consent, were randomly sampled for brain imaging with a standardized MRI protocol (HUNT-MRI). Participants that had previously participated in HUNT1, 2 and 3, and lived maximally 45 minutes away by car or public transport from Levanger hospital where the scanning was performed were eligible for inclusion. Individuals exhibiting standard safety contraindication to MRI, i.e. pacemaker, severe claustrophobia or body weight above 150 kg, were excluded. Details about the recruitment of participants to the HUNT-MRI study and the imaging procedure have been published previously(16, 17) and a comparison of the non-invited, the non-participants and the participants of the HUNT-MRI study revealed that they were not widely different from the general population, with the possible exception of somewhat reduced cardiovascular risk factors(16).

MRI scanning

All imaging was performed on the same 1.5 T General Electric Signa HDx 1.5 T MRI scanner equipped with an eight channel head coil and software version pre-14.0M (GE Healthcare). Scans included a T1 weighted volume, transverse T2, T2* and FLAIR sequences, a time of flight 3D angio sequence through the base of the brain and diffusion tensor imaging (DTI). The T1 weighted volumes/3D scans and the T2 images were used in the present study.

MRI analysis

The T1 weighted volumes were analysed using FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/) and measurements of the volumes of the subcortical nuclei accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus were obtained using an automated procedure described previously(18). The data on volume were imported into SPSS where the statistical analyses were performed. To avoid bias, all FreeSurfer results were visually inspected by a blinded colleague at the multimodal Imaging Lab, University of California, San Diego, where the data analysis was performed, and all subpar data sets removed. The volumes of the different nuclei were combined for the right and left hemisphere to constitute the total volume of the specified nucleus.

Local shape differences were compared between groups using a vertex-by-vertex analysis based on FMRIB's Integrated Registration and Segmentation Tool (FIRST) 1.2 (19). First, a surface mesh of the different nuclei in each subject was created using a deformable mesh model composed of a set of vertices. The number of vertices was then fixed so that corresponding vertices could be compared between groups(20). The surface for the right and left nuclei of each participant were then aligned to an average model provided by FIRST using a 6-degrees of freedom transformation. Group differences in the surface displacement maps were analyzed in FMRIB Software Library using randomize for nonparametric permutation-based inference (n = 5000) with a threshold at $P<0.05$ and corrected using threshold-free cluster enhancement(21).

Intracranial volume (ICV) estimation was performed in Statistical Parametric Mapping 8 (SPM8) (rel. 5236) (http://www.fil.ion.ucl.ac.uk/spm/) using an automated version of the reverse brain mask method (RBM) (22, 23). ICV corrections using the residuals method were applied in all volume analyses.

Headache diagnoses

Participants of the HUNT study had answered headache questionnaires as part of both the HUNT2 and HUNT3 surveys. In both surveys the headache questionnaires started with a screening question “Have you suffered from headache during the last 12 months?” and participants answering “yes” were classified as headache sufferers. The accuracy of being a headache sufferer was evaluated showing a sensitivity of 85 % and a specificity of 83 % in HUNT2 and a sensitivity of 88 % and a specificity of 86 % in HUNT3(24, 25).

In the HUNT3 survey the headache sufferers were further categorized into three mutually exclusive headache categories: migraine, TTH ≥ 1 day per month and unclassified

headache. The migraine and TTH diagnoses were based on the criteria of the 2nd edition of the International Classification of Headache Disorders (ICHD-II). The classification and accuracy of the questionnaire-based diagnoses have been described previously(24). For migraine the sensitivity was 51 % and specificity 95 % whereas for TTH the respective values were 96 % and 69 %. Headache sufferers not fulfilling the criteria of either migraine or TTH were categorized as having unclassified headache. In the present study no specific analyses were conducted based on this group. In addition the headache sufferers in HUNT3 were categorized into two different groups based on frequency of headache attacks (< 7 days/month and >= 7 days/month).

The HUNT2 questionnaire lacked information regarding the strength of the headache and thus the diagnoses were not strictly according to the ICHD-criteria. The liberal migraine diagnosis from the validation study(25) was applied showing a sensitivity of 49 % and a specificity of 96 %. Individuals not fulfilling the criteria for this diagnosis were classified as non-migraineurs. The fact that 780 (78 %) participants had answered the headache questionnaire in both HUNT2 and HUNT3 made it possible to classify individuals in four groups according to when they did or did not suffer from headache: headache only HUNT2, headache only HUNT3, headache in both HUNT2 and 3 and no headache suffering in either HUNT2 or 3. The last group consisted of those answering “no” to the screening question in both surveys and was used as controls.

Potential confounders

Because they are all associated to both headache and brain morphology, the following variables were included as potential confounders: age(26, 27), sex(26, 28), alcohol use(29, 30) and blood pressure(31, 32). All participants in HUNT3 had their blood pressure measured three times. The mean arterial pressure was calculated as a mean of the second and third measurement. The alcohol variable was divided into 8 different groups with regard to the frequency of consumption the last year (4-7 times/week; 2-3 times/week; once a week; 2-3 times/month; once a month; few times last year; never within last year; never consumed alcohol). Data on blood pressure and alcohol consumption from HUNT2 were not considered because of the relatively long time interval between the data collection (1995-1997) and MRI scanning (2007-2009) and because of a higher fraction of missing data than in the HUNT3 survey.

Statistics

Volumes of the subcortical structures for the different headache groups were compared one-on-one to headache non-sufferers using analysis of covariance (ANCOVA). The statistical model had volume of a subcortical structure as the continuous dependent variable and headache status as independent variable. In addition to the aforementioned potential confounders, ICV was corrected for using the residuals method(33). Effect sizes for the volume comparisons were calculated using Cohen's d. When analysing the hypothesis, individuals suffering from headache in HUNT3, regardless of subtype, were compared to the control group, i.e. headache in neither HUNT2 nor HUNT3. In order to examine a dose-response relationship those with frequent headache in HUNT3 (>=7 days/month) were compared to those with infrequent headache (<7 days/month) using the same statistical model with covariates as described above. To elucidate the possible contribution of outliers, an analysis with the removal of individuals deviating > 1.5 x interquartile range above or below the third and first quartile respectively was conducted.

The comparisons of volume data were tested with a significance threshold set to $P<0.05$, two-tailed. This was done when testing the hypothesis and in the exploratory analyses to minimize the risk of type II error. Group differences in the surface displacement maps were thresholded at $P<0.05$, two-tailed, and corrected using threshold-free cluster enhancement. This was true for both the hypothesis and the exploratory analyses. SPSS version 21 (SPSS IBM, New York, U.S.A.) was used for the volume analyses and the shape data were analysed with the FMRIB Software.

Post hoc analyses

The most significant group difference was increased caudate and putamen volumes in the non-migrainous headache groups. We have previously shown, in the present population, that white matter hyperintensities is more common in TTH(17). Since white matter hyperintensities alter image contrast, post hoc analyses on the association between white matter hyperintensity load, as described by Fazeka's score(17), and the volume of the caudate and the putamen were performed. The ANOVA analyses had volume of the caudate and the putamen (corrected for ICV using the residuals method) as the continuous dependent variable and the Fazeka's score as the ordinal independent variable. In addition the analyses were rerun corrected for having headache or not.

Results

Of the 1006 participants in HUNT-MRI, 21 individuals were excluded from the present study because of subcortical pathology (Figure 1). Individuals who exhibited pathology of only the cerebral cortical mantle (n=23) were not excluded. Furthermore MRI data from 67 individuals were not included in the analyses owing to poor image quality (mostly motion artefacts) or other errors in the image data acquisition incompatible with the FreeSurfer algorithm (Figure 1). Of the remaining 918 individuals, 814 had answered the headache questionnaire in HUNT2, 783 in HUNT3 and 709 had answered the headache questionnaires in both HUNT2 and HUNT3 (Figure 1). In addition some individuals were excluded because of lack of data on ICV, alcohol consumption and blood pressure (Figure 1).

Results on headache and volume of subcortical structures of the brain are provided in Table 1. The volume of the accumbens was similar in headache sufferers in HUNT3 (1040.37 mm^3) and headache non-sufferers in HUNT2 and HUNT3 (1051.68 mm^3) (P=0.93). No difference in shape of the accumbens between the headache and control group was found. Thus, our hypothesis was not confirmed.

In the exploratory analyses, compared to headache non-sufferers, the caudate was significantly larger in those suffering from headache in HUNT3 (P=0.005), both HUNT2 and HUNT3 (P=0.007) and only HUNT3 (P=0.007), but significantly smaller in headache sufferers in HUNT2 (P=0.02). When examining the headache diagnoses, those with TTH in HUNT3 (P<0.001) and those with non-migrainous headache in HUNT2 (P=0.03) had larger volume of caudate. In addition a significantly larger putamen was found in those with headache in both HUNT2 and HUNT3 (P=0.03) and TTH in HUNT3 (P=0.04). Most effect sizes were very small to small (range: <0.01-0.35, mean=0.13 and median=0.13) and especially for the comparisons showing significant results (range: <0.01-29, mean=0.11, median=0.04).

Concurring with the volume analyses, between group comparisons of vertex-wise nucleus shape demonstrated regionally deformation of the putamen in TTH in HUNT3 and headache in both HUNT2 and HUNT3. In addition shape difference without volume difference of the putamen was present in the following groups: headache in HUNT3, headache in HUNT2, non-migrainous headache in HUNT2 and migraine in HUNT2. More specifically the headache sufferers displayed an expansion located laterally and present in both the left and right putamen (Figure 2). Those suffering from migraine in HUNT2 had very

limited shape deformation in two small areas (6 and 10 voxels) in the accumbens compared to headache non-sufferers.

Headache frequency, expressed as number of headache days per month, was positively associated with the volume of both caudate (P=0.009) and putamen (P=0.04) (Table 2). The analyses where outliers were removed gave higher p-values for all previously significant comparison leading to non-significant results of headache in HUNT2 (caudate, P=0.06), non-migrainous headache in HUNT2 (caudate, P=0.05) and TTH in HUNT3 (putamen, P=0.05). Further, after removing outliers, headache sufferers in HUNT3 (P=0.01) and in both HUNT2 and HUNT3 (P=0.01) were found to have smaller volume of the caudate instead of larger.

Post hoc analyses

The post hoc analyses showed that the Fazeka's score was positively associated to the volume of the caudate (F (3,908)=21.02 and $P<0.001$) (Figure 3), but not to the volume of the putamen (F (3,908)=0.08 and $P=0.97$). Similar results were obtained (caudate: $P<0.001$; putamen: $P=0.97$) when the analyses were corrected for having headache or not.

Discussion

The present study failed to confirm our hypothesis that headache sufferers would have smaller volume and deformation of the accumbens compared to headache non-sufferers. The exploratory analyses gave some significant albeit inconsistent results, which may be useful for generating hypotheses in future studies. These results showed that headache sufferers have different volume of the dorsal striatum (caudate and putamen) compared to headache non-sufferers. Larger or smaller volume of caudate was present among all headache groups except for the two migraine groups and those suffering from headache in only HUNT2. Those suffering from headache in HUNT2 were found to have smaller volume of the caudate whereas the other headache groups displayed larger volumes. In addition larger volume and shape expansion of the putamen was found in those with TTH in HUNT3 and headache in both HUNT2 and HUNT3. Deformation of the putamen, without volume difference, was also detected in several headache groups in both HUNT2 and HUNT3. The effect sizes for the volume analyses were very small to small indicating limited impact of headache status on volume of subcortical nuclei in adults in the general population. Furthermore, when removing outliers all previous significant *P*-values became larger and the results more inconsistent. The two areas in the accumbens showing shape deformation among those with migraine in

HUNT2 were extremely small and the present authors consider them to be of no relevance.

There are several strengths of the present study. Firstly, to our knowledge this is the first population-based imaging study relating subcortical structures to headache. The participants were randomly drawn among individuals attending a large longitudinal epidemiological study (HUNT), thereby avoiding potential selection bias of clinic-based studies. Secondly, headache sufferers were categorized into different headache categories allowing for investigation of associations between different types of headache and subcortical volumes. The headache criteria used in this study have been validated showing acceptable accuracy(24). The migraine diagnoses were highly specific, but had lower sensitivity. This relationship was opposite for the non-migrainous headache diagnoses, hence we have probably classified some true migraineurs as non-migraineurs. Such misclassification will diminish rather than increase differences between the headache groups. Thirdly, the brain morphology was determined with a fully automated method, in which there is no risk of measurement bias related to interpretation of images by humans. SBM has been proven to be a sensitive and reliable method in examining brain dimensions when compared to histological and manual measurement(34, 35). Fourthly, before running the analyses we postulated a precise hypothesis based on previous findings in order to enable definite conclusions. In addition exploratory analyses with the purpose of generating hypotheses for later studies were performed. Fifthly, data on headache status in HUNT2 and HUNT3 allowed selection of individuals with documented very little to no headache complaints over several years as control group. Last but not least, compared to the previous clinic-based studies this population-based study was superior in terms of number of both headache sufferers and controls.

The most prominent limitation in this study is the relatively long time interval from the participants answered the headache questionnaire (1995-1997 in HUNT 2 and 2006-2008 in HUNT 3) to when they were scanned (2007-2009). Morphological changes can both arise and recede within a year(6, 36). Although this effect cannot be ruled out it seems unlikely that the headache had improved or increased dramatically in the majority during the 1-2 years from the HUNT3 questionnaire to the MRI scanning. Furthermore longitudinal data existed only on headache status and therefore the present study does not allow conclusions as to whether differences in subcortical morphology may be cause or consequence of headache. Even though it is fair to assume individuals with consistent answers in the two surveys to be long-term headache sufferers and long-term non-sufferers, caution in interpretation of these results has to be taken because of the lack of information on headache status between the two

time points. Also estimating the headache status of individuals with a questionnaire is inferior to a clinical interview.

The present study concurs to some extent with previous studies, finding both bigger and smaller volume of the caudate and putamen in migraineurs(4, 8, 9). However, in this study headache sufferers in general displayed significant volume differences in the two subcortical nuclei. Before concluding that headache sufferers in general exhibit such a brain structural variation, one should remember that the results obtained in the present sample were partially due to outliers and somewhat inconsistent showing headache sufferers to have both larger and smaller volume of caudate. Furthermore, the effect sizes were small for all the significant comparisons indicating that if the results are true the volume of the caudate and the putamen are almost indistinguishable between headache sufferers and non-sufferers in the general population.

In contrast to previous studies(4, 8, 9), the present results indicate that non-migrainous types of headache, such as TTH, are more strongly associated to structural deviation of at least the caudate than migraine is. Indeed, our data showed that migraineurs tended to have smaller volume of caudate and putamen but considering the effect sizes the lack of significance regarding the migraine groups could be caused by lack of power. However, the present migraine group was larger than the ones in previous studies. Based on the sensitivity and specificity of the present diagnoses, the TTH group probably included some individuals with migraine and thus volume of the caudate and putamen may in reality be even more strongly associated with TTH. The present analyses indicated that temporal proximity is important for the association between headache and volume of caudate, since those who had headache a relatively short time before the MRI scanning (HUNT3) had a larger caudate than those who had headache only in the past (HUNT2).

The subcortical nuclei shape analyses showed lateral parts of the bilateral putamen to be expanded in headache sufferers, but not in the two migraine groups. It seems reasonable to hypothesize that the global difference in volume of putamen is attributed to these regionally morphological changes. No difference in shape was detected between headache sufferers and non-sufferers for the caudate, indicating a more evenly distributed volume increase in headache sufferers in this nucleus.

The caudate and putamen constituting the dorsal striatum receive input from the cerebral cortex and thalamus and activation here enables execution of motor and cognitive cerebral programs(37, 38). Hence, one may speculate that this region is larger due to an increase in afferent/efferent signalling as part of headache pathophysiology. On the other

hand, the post hoc analyses showing a highly significant correlation between Fazeka's score and caudate volume may indicate that the dorsal striatum volume increase in headache sufferers represents a MRI artefact caused by white matter hyperintensities. The relationship between white matter hyperintensities and caudate volume was not confounded by headache status, as correction for headache status did not eliminate the association. Conceivably changes in the nearby white matter alter the grey/white matter contrast and subsequently apparent grey matter volume size in T1 weighted MRI scans. It has previously been demonstrated, both in this population and in others, that white matter hyperintensities are more common in headache sufferers(17, 39).

The exact interpretation of differences in deep grey matter nucleus volume seen on MRI remains to be fully understood but the hypothesis that it may arise from white matter changes should be further explored. As in headache brain MRI studies, studies of other pain-related conditions have showed volumes of putamen and caudate to be both larger(40-42) and smaller(43, 44) than in controls, but since chronic pain also has been associated to white matter hyperintensities(45) these findings too could be caused by changes in the white matter. The current findings in this headache population could therefore be of relevance for other pain conditions as well.

In conclusion the present large population-based imaging study failed to confirm our hypothesis that headache sufferers exhibit smaller volume and different shape of accumbens. Instead we found headache sufferers to have somewhat different volume of the dorsal striatum, especially caudate, compared to non-sufferers, but post hoc analyses showed that this could be explained by white matter hyperintensities. Overall the effect sizes were very small and the results were somewhat inconsistent and partially due to outliers. Hence in the general population, there are probably very small differences in the volumes of subcortical nuclei between headache sufferers and non-sufferers.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

[1] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(2012):2163-96.

[2] Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. Lancet neurology. 2008;7(2008):354-61.

[3] Jacobs B, Dussor G. Neurovascular contributions to migraine: Moving beyond vasodilation. Neuroscience. 2016;338(2016):130-44.

[4] Yuan K, Zhao L, Cheng P, Yu D, Zhao L, Dong T, et al. Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. J Pain. 2013;14(2013):836-44.

[5] Maleki N, Becerra L, Brawn J, McEwen B, Burstein R, Borsook D. Common hippocampal structural and functional changes in migraine. Brain structure & function. 2013;218(2013):903-12.

[6] Liu J, Lan L, Li G, Yan X, Nan J, Xiong S, et al. Migraine-related gray matter and white matter changes at a 1-year follow-up evaluation. J Pain. 2013;14(2013):1703-8.

[7] Magon S, May A, Stankewitz A, Goadsby PJ, Tso AR, Ashina M, et al. Morphological Abnormalities of Thalamic Subnuclei in Migraine: A Multicenter MRI Study at 3 Tesla. J Neurosci. 2015;35(2015):13800-6.

[8] Maleki N, Becerra L, Nutile L, Pendse G, Brawn J, Bigal M, et al. Migraine attacks the Basal Ganglia. Molecular pain. 2011;7(2011):71.

[9] Rocca MA, Messina R, Colombo B, Falini A, Comi G, Filippi M. Structural brain MRI abnormalities in pediatric patients with migraine. Journal of neurology. 2014;261(2014):350-7.

[10] Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, et al. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J Pain. 2013;14(2013):663-75.

[11] Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. Hum Reprod Update. 2014;20(2014):737-47.

[12] Mitsi V, Zachariou V. Modulation of pain, nociception, and analgesia by the brain reward center. Neuroscience. 2016(2016).

[13] Dias EV, Sartori CR, Mariao PR, Vieira AS, Camargo LC, Athie MC, et al. Nucleus accumbens dopaminergic neurotransmission switches its modulatory action in chronification of inflammatory hyperalgesia. Eur J Neurosci. 2015;42(2015):2380-9.

[14] Elvemo NA, Landro NI, Borchgrevink PC, Haberg AK. Reward responsiveness in patients with chronic pain. Eur J Pain. 2015;19(2015):1537-43.

[15] DaSilva AF, Nascimento TD, Love T, DosSantos MF, Martikainen IK, Cummiford CM, et al. 3D-neuronavigation in vivo through a patient's brain during a spontaneous migraine headache. Journal of visualized experiments : JoVE. 2014(2014).

[16] Honningsvag LM, Linde M, Haberg A, Stovner LJ, Hagen K. Does health differ between participants and non-participants in the MRI-HUNT study, a population based neuroimaging study? The Nord-Trondelag health studies 1984-2009. BMC medical imaging. 2012;12(2012):23.

[17] Honningsvag LM, Hagen K, Haberg A, Stovner LJ, Linde M. Intracranial abnormalities and headache: A population-based imaging study (HUNT MRI). Cephalalgia : an international journal of headache. 2015(2015).

[18] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(2002):341-55.

[19] Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage. 2011;56(2011):907-22.

[20] Lim HK, Hong SC, Jung WS, Ahn KJ, Won WY, Hahn C, et al. Hippocampal shape and cognitive performance in amnestic mild cognitive impairment. Neuroreport. 2012;23(2012):364-8.

[21] Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 2009;44(2009):83-98.

[22] Keihaninejad S, Heckemann RA, Fagiolo G, Symms MR, Hajnal JV, Hammers A. A robust method to estimate the intracranial volume across MRI field strengths (1.5T and 3T). Neuroimage. 2010;50(2010):1427-37.

[23] Hansen TI, Brezova V, Eikenes L, Håberg AK, Vangberg TR. How does the accuracy of intracranial volume measurements affect normalized brain volumes? Sample size estimates based on 966 subjects from the HUNT MRI cohort. AJNR American journal of neuroradiology. Forthcoming 2015(Forthcoming 2015).

[24] Hagen K, Zwart JA, Aamodt AH, Nilsen KB, Brathen G, Helde G, et al. The validity of questionnaire-based diagnoses: the third Nord-Trondelag Health Study 2006-2008. The journal of headache and pain. 2010;11(2010):67-73.
[25] Hagen K, Zwart JA, Vatten L, Stovner LJ, Bovim G. Head-HUNT: validity and reliability of a headache questionnaire in a large population-based study in Norway. Cephalalgia : an international journal of headache. 2000;20(2000):244-51.
[26] Linde M, Stovner LJ, Zwart JA, Hagen K. Time trends in the prevalence of headache disorders. The Nord-Trondelag Health Studies (HUNT 2 and HUNT 3). Cephalalgia : an international journal of headache. 2011;31(2011):585-96.
[27] Farrell MJ. Age-related changes in the structure and function of brain regions involved in pain processing. Pain Med. 2012;13 Suppl 2(2012):S37-43.
[28] Ruigrok AN, Salimi-Khorshidi G, Lai MC, Baron-Cohen S, Lombardo MV, Tait RJ, Suckling J. A meta-analysis of sex differences in human brain structure. Neurosci Biobehav Rev. 2014;39(2014):34-50.
[29] Aamodt AH, Stovner LJ, Hagen K, Brathen G, Zwart J. Headache prevalence related to smoking and alcohol use. The Head-HUNT Study. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2006;13(2006):1233-8.
[30] Buhler M, Mann K. Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcohol Clin Exp Res. 2011;35(2011):1771-93.
[31] Hagen K, Stovner LJ, Vatten L, Holmen J, Zwart JA, Bovim G. Blood pressure and risk of headache: a prospective study of 22 685 adults in Norway. J Neurol Neurosurg Psychiatry. 2002;72(2002):463-6.
[32] Beauchet O, Celle S, Roche F, Bartha R, Montero-Odasso M, Allali G, Annweiler C. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. J Hypertens. 2013;31(2013):1502-16.
[33] Barnes J, Ridgway GR, Bartlett J, Henley SM, Lehmann M, Hobbs N, et al. Head size, age and gender adjustment in MRI studies: a necessary nuisance? Neuroimage. 2010;53(2010):1244-55.
[34] Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology. 2002;58(2002):695-701.
[35] Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry. 2003;60(2003):878-88.
[36] Teutsch S, Herken W, Bingel U, Schoell E, May A. Changes in brain gray matter due to repetitive painful stimulation. Neuroimage. 2008;42(2008):845-9.
[37] Lanciego Jé L, Luquin N, Obeso Jé A. Functional Neuroanatomy of the Basal Ganglia. Cold Spring Harb Perspect Med. 2012;2(2012).
[38] Arsalidou M, Duerden EG, Taylor MJ. The centre of the brain: topographical model of motor, cognitive, affective, and somatosensory functions of the basal ganglia. Hum Brain Mapp. 2013;34(2013):3031-54.
[39] Kurth T, Mohamed S, Maillard P, Zhu Y-C, Chabriat H, Mazoyer B, et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. BMJ. 2011;342(2011).
[40] Mao C, Wei L, Zhang Q, Liao X, Yang X, Zhang M. Differences in brain structure in patients with distinct sites of chronic pain: A voxel-based morphometric analysis. Neural regeneration research. 2013;8(2013):2981-90.
[41] Wu Q, Inman RD, Davis KD. Neuropathic pain in ankylosing spondylitis: a psychophysics and brain imaging study. Arthritis Rheum. 2013;65(2013):1494-503.
[42] Schmidt-Wilcke T, Luerding R, Weigand T, Jurgens T, Schuierer G, Leinisch E, Bogdahn U. Striatal grey matter increase in patients suffering from fibromyalgia--a voxel-based morphometry study. Pain. 2007;132 Suppl 1(2007):S109-16.
[43] Mao CP, Bai ZL, Zhang XN, Zhang QJ, Zhang L. Abnormal Subcortical Brain Morphology in Patients with Knee Osteoarthritis: A Cross-sectional Study. Front Aging Neurosci. 2016;8(2016):3.
[44] Luchtmann M, Steinecke Y, Baecke S, Lutzkendorf R, Bernarding J, Kohl J, et al. Structural brain alterations in patients with lumbar disc herniation: a preliminary study. PloS one. 2014;9(2014):e90816.
[45] Buckalew N, Haut MW, Aizenstein H, Rosano C, Edelman KD, Perera S, et al. White matter hyperintensity burden and disability in older adults: is chronic pain a contributor? PM & R : the journal of injury, function, and rehabilitation. 2013;5(2013):471-80; quiz 80.

Table 1. Association between volume (mm^3) of subcortical grey matter nuclei and headache status in HUNT2 and HUNT3 corrected for intracranial volume, sex, age, blood pressure and alcohol use.

		Accumbens	Amygdala	Caudate	Hippocampus	Pallidum	Putamen	Thalamus
Headache non sufferers HUNT2+3 n=308	Mean (SD)	1051.68 (202.88)	2767.67 (441.77)	7068.07 (896.58)	7675.47 (772.23)	3160.71 (394.98)	10176.85 (1225.96)	12980.90 (1382.47)
Headache sufferers HUNT3 n=276	Mean (SD)	1040.37 (206.27)	2685.80 (397.85)	**7087.44 (1061.70)**	7541.70 (813.39)	3120.43 (435.07)	10195.73 (1316.52)	12799.53 (1426.46)
	P-value	0.93	0.70	**0.005**	0.72	0.40	0.07	0.37
	Cohen's d	0.06	0.19	**0.02**	0.17	0.10	0.01	0.13
Migraine HUNT3 n=76	Mean (SD)	1014.44 (220.70)	2642.98 (425.83)	6763.07 (893.24)	7391.92 (816.27)	3046.85 (441.86)	9978.48 (1339.56)	12588.89 (1477.76)
	P-value	0.48	0.66	0.82	0.13	0.87	0.91	0.97
	Cohen's d	0.18	0.29	0.34	0.36	0.27	0.15	0.27
TTH HUNT3 n=85	Mean (SD)	1043.67 (203.70)	2697.92 (321.78)	**7362.76 (1126.56)**	7602.41 (777.98)	3159.20 (430.89)	**10388.35 (1235.99)**	12894.46 (1435.14)
	P-value	0.89	0.55	**<0.001**	0.94	0.31	**0.04**	0.51
	Cohen's d	0.04	0.18	**0.29**	0.09	<0.01	**0.17**	0.06
Headache sufferers HUNT2 n=384	Mean (SD)	1040.00 (205.65)	2683.17 (424.18)	**7039.89 (1034.47)**	7532.41 (817.72)	3072.88 (435.07)	10145.31 (1299.63)	12864.80 (1443.77)
	P-value	0.72	0.85	**0.02**	0.92	0.58	0.09	0.05
	Cohen's d	0.06	0.20	**0.03**	0.18	0.21	0.02	0.08
Migraine HUNT2 n=142	Mean (SD)	1028.67 (207.95)	2672.39 (418.05)	6942.00 (887.74)	7675.87 (852.74)	3084.33 (423.84)	10142.29 (1284.64)	12737.68 (1441.38)
	P-value	0.91	0.81	0.17	0.56	0.72	0.09	0.23
	Cohen's d	0.11	0.22	0.14	<0.01	0.19	0.03	0.17
Non-migraine HUNT2 n=242	Mean (SD)	1046.64 (204.43)	2689.50 (428.48)	**7097.32 (1109.33)**	7570.28 (795.83)	3066.16 (442.25)	10147.08 (1311.00)	12939.40 (1442.93)
	P-value	0.75	0.55	**0.03**	0.90	0.26	0.32	0.10
	Cohen's d	0.02	0.18	**0.03**	0.13	0.23	0.02	0.03
Headache sufferers HUNT2+3 n=205	Mean (SD)	1051.41 (198.56)	2677.76 (404.24)	**7072.96 (1087.53)**	7497.76 (833.43)	3109.18 (455.15)	**10237.04 (1336.67)**	12793.36 (1429.46)
	P-value	0.43	0.68	**0.007**	0.43	0.52	**0.03**	0.28
	Cohen's d	<0.01	0.21	**<0.01**	0.22	0.12	**0.05**	0.13
Headache sufferers only HUNT2 n=131	Mean (SD)	1017.09 (205.10)	2650.20 (411.85)	6939.17 (977.96)	7546.35 (779.09)	3050.61 (420.79)	9971.06 (1273.92)	12863.53 (1382.32)
	P-value	0.48	0.35	0.80	0.94	0.20	0.85	0.21
	Cohen's d	0.17	0.28	0.14	0.17	0.27	0.16	0.08
Headache sufferers only HUNT3 n=51	Mean (SD)	1031.92 (223.71)	2735.52 (408.68)	**7298.50 (959.59)**	7732.64 (710.16)	3213.23 (353.18)	10199.92 (1159.87)	13007.74 (1490.42)
	P-value	0.58	0.99	**0.007**	0.36	0.11	0.66	0.44
	Cohen's d	0.09	0.08	**0.25**	0.08	0.14	0.02	0.02

Table 2. Frequency of headache in HUNT3 and volumes of subcortical grey matter nuclei.

Subcortical structure	**Headache non sufferers HUNT2+3 n=494**	**Headache <7 days/month n=226**	**Headache >=7 days/month n=49**	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**P-value**
Accumbens	1032.13 (202.87)	1040.00 (209.65)	1045.64 (192.46)	0.36
Amygdala	2719.32 (426.84)	2693.69 (397.99)	2664.07 (390.97)	0.85
Caudate	7009.75 (933.84)	7097.56 (992.36)	7072.67 (1338.01)	**0.009**
Hippocampus	7611.70 (785.55)	7563.40 (802.64)	7481.57 (827.54)	0.99
Pallidum	3113.37 (411.71)	3123.43 (432.19)	3106.16 (456.75)	0.21
Putamen	10077.46 (1239.53)	10196.60 (1366.04)	10210.33 (1366.04)	**0.04**
Thalamus	12911.63 (1390.52)	12834.48 (1391.70)	12676.77 (1575.92)	0.77

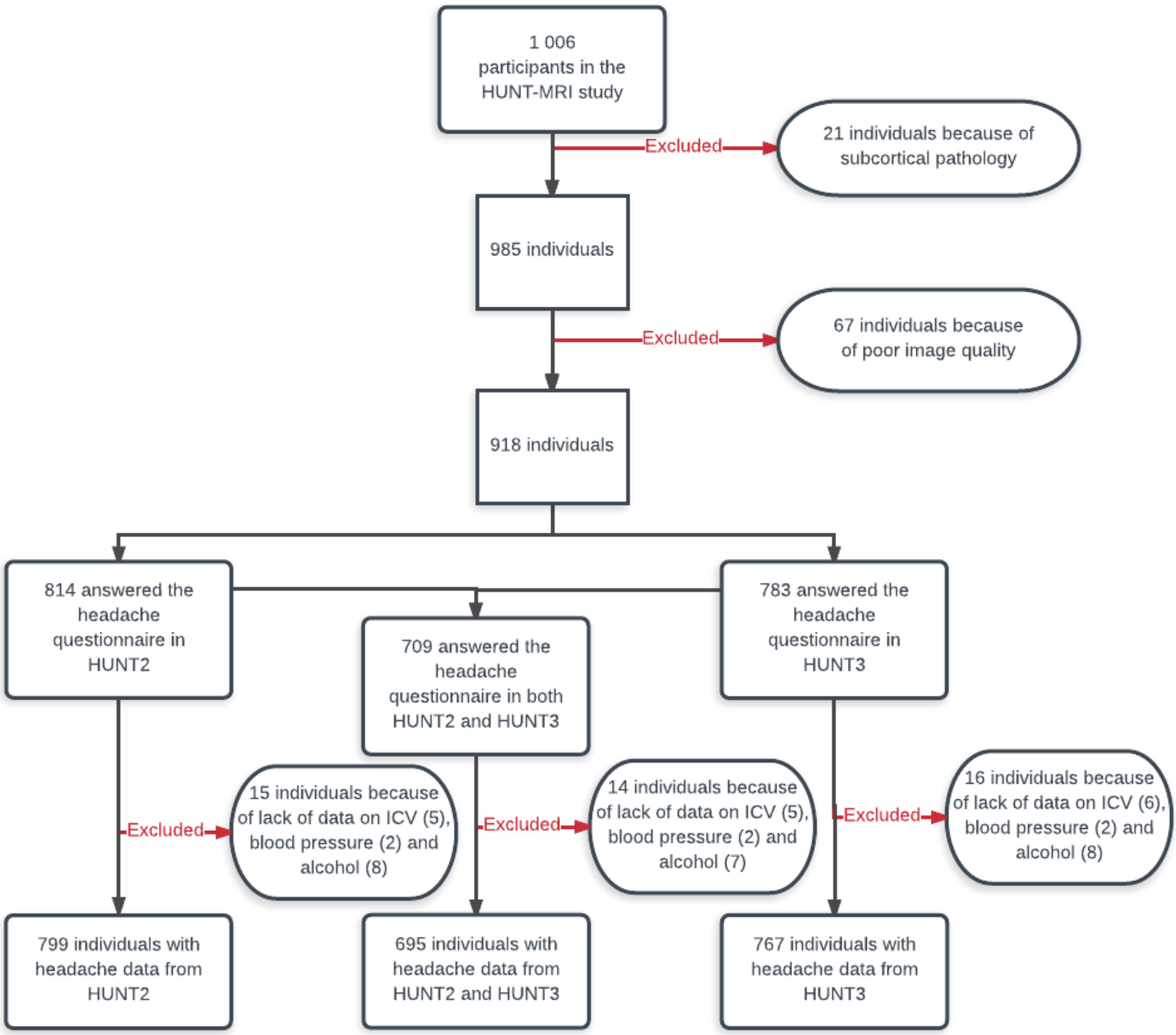

Figure 1. Flowchart of participation in the HUNT-MRI study

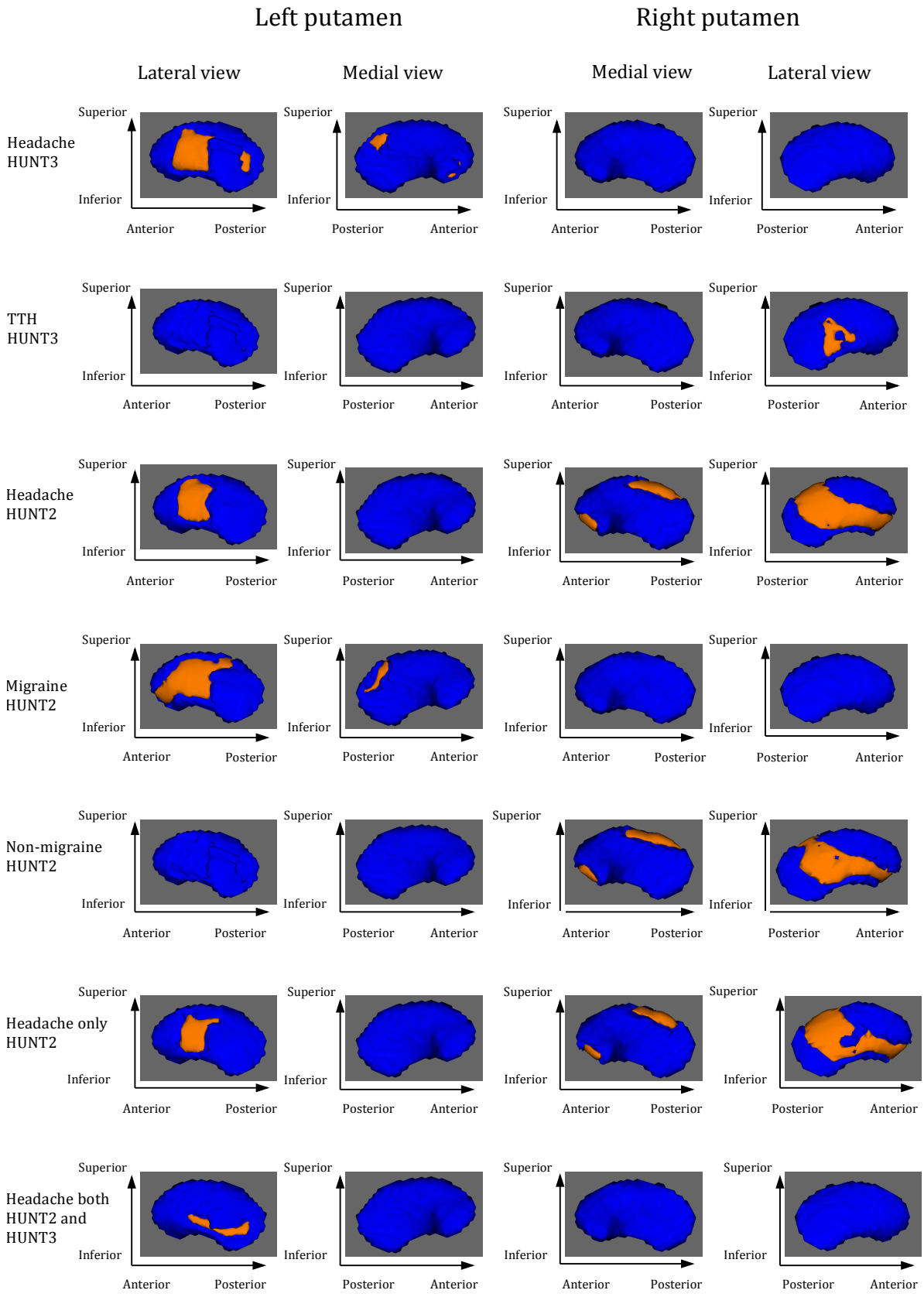

Figure 2. Putaminal shape differences. Different headache groups compared to controls (headache non-sufferers in HUNT2 and HUNT3). Areas of significant difference ($P<0.05$ corrected with the threshold-free cluster enhancement) are shown in orange. The headache groups "Migraine HUNT3" and "Headache only HUNT3" did not show any difference in shape compared to the control group and are therefore not included in the figure.

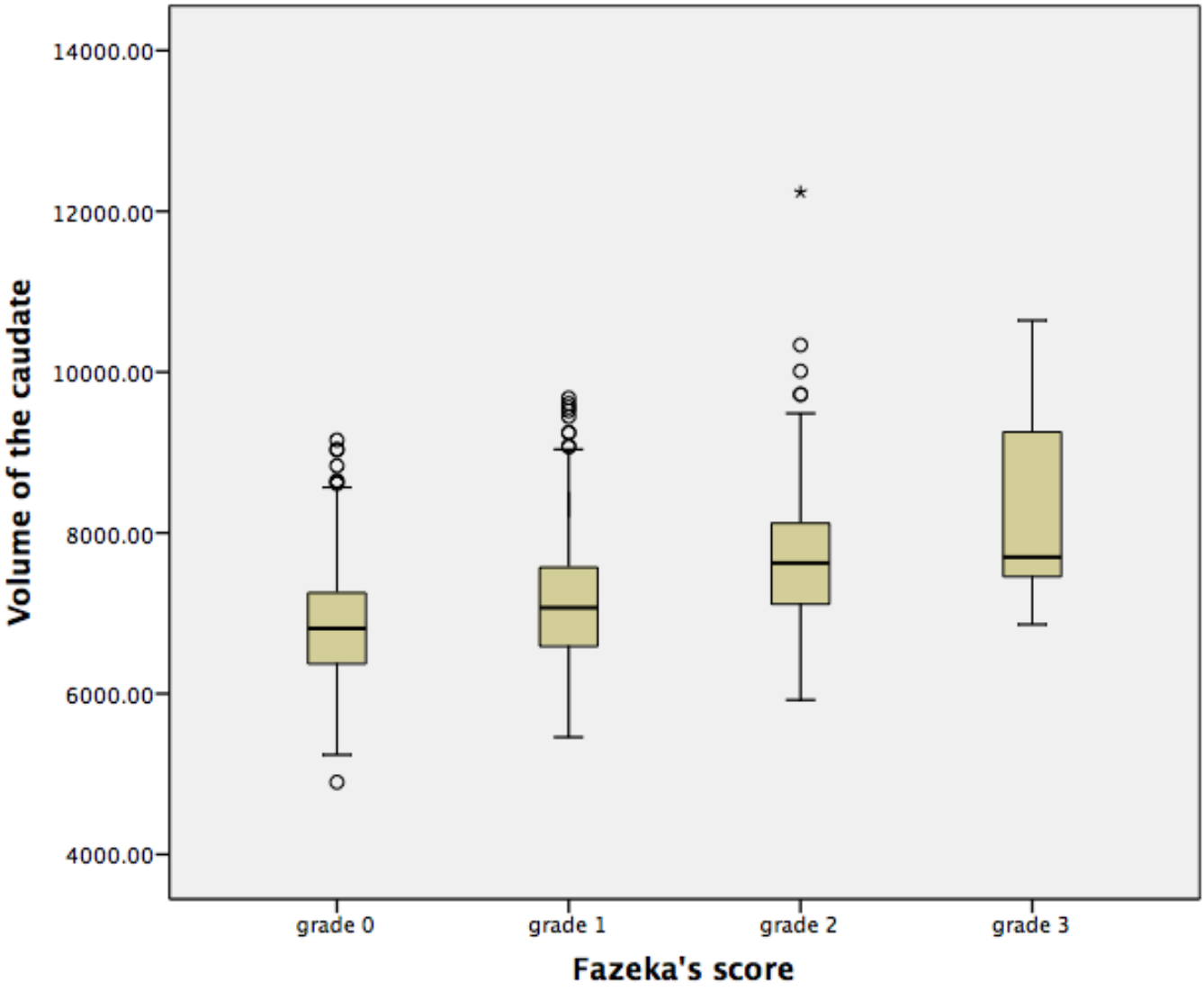

Figure 3. Comparing of the volume of the caudate (mm^3) with different grades of the Fazeka's score.