

“Visualization” of Pain using Cerebral 18 F-FDG PET/CT Following Surgical Treatment of Lumbar Disc Herniation

Christian Christensen Støttrup

Lillebaelt Hospital

Caius Constantinescu

Odense University Hospital

Reza Piri

Odense University Hospital

Mohsen Khosravi

Thomas Jefferson University

Andrew Newberg

Thomas Jefferson University

Mikkel Østerheden Andersen

Lillebaelt Hospital

Abass Alavi

Thomas Jefferson University

Poul Flemming Høilund-Carlson (✉ pfhc@rsyd.dk)

Odense University Hospital

Research Article

Keywords: Pain , Pain perception , PET , 18F-FDG , Lumbar disc herniation , Thalamus , Quantification

Posted Date: August 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-745097/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

We hypothesised that unilateral leg pain following surgical treatment of lumbar disc herniation (LDH) is associated with an increase in the glucose metabolism of the contralateral thalamus. Patients scheduled for surgery due to LDH underwent ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) less than two weeks prior to surgery. Their thalamic FDG uptake was measured and expressed as the mean and partial volume corrected mean standardized uptake values (SUVmean and cSUVmean). These measures were compared with patient-related outcome measures collected pre- and 1-year postoperatively: back and leg pain on a 0-100 VAS scale and health related quality of life as measured by the EuroQol-5D (EQ-5D). Twenty-six patients (10 females) aged 49.7 ± 7.4 (mean \pm SD) years were included. There was a significant correlation between painful body side and increased contralateral thalamic uptake of FDG, with regard to cSUVmean values. Correlation analyses including clinical parameters and cSUVmean indicated some association with 1-year change in EQ-5D. These preliminary data sustain the hypothesis that unilateral pain in patients with LDH is associated with increased glucose metabolism in the contralateral thalamus, suggestion a central role of thalamus in chronic pain perception.

Introduction

In modern society, pain symptoms may lead to great morbidity among patients. Many pain conditions require medication that often leads to the use and even abuse of opioids. The latter “spillover effect” further burdens the healthcare system with chronically afflicted patients and leads to severe cost expenditure for individuals and society ¹⁻³. We do not really know what pain is but are aware that pain conditions have a negative impact on most individuals’ physical and psychosocial health. Consequently, research in pain and its management aim for a better understanding of pain and pain perception. In addition, there is a need for a quantifiable measure to compare pain between individuals and monitor effects of pain therapy.

With modern imaging techniques we are able to assess and even quantify nutrient uptake in cells, thereby obtaining a measure of cell metabolism. In the nervous system, and particularly in the brain, changes in regional cellular metabolism are supposed to reflect changes in cerebral functional activity. In a former study by Newberg et al. single-photon emission computed tomography (SPECT) was used to analyze cerebral blood flow in patients with chronic pain conditions ⁴. Their findings indicated that following acupuncture therapy, cerebral blood flow changed in the frontal lobes and the thalami. These changes were thought to correlate with pain perception of the patients and, therefore, were suggested as a surrogate measure of quantifiable pain perception.

Patients with lumbar disc herniation (LDH) have primarily unilateral pain radiating to one of their legs. This unilateral pattern creates the foundation for comparing how pain stimuli affect brain cell metabolism across the two hemispheres. We hypothesized that unilateral pain of LDH patients will increase metabolism in the thalamus of the contralateral hemisphere and be detectible by positron

emission tomography/computed tomography with ^{18}F -fluorodeoxyglucose (FDG-PET/CT). Furthermore, that such visualization would be quantifiable and correlate with patient-reported pain perception and clinical outcome measures.

Results

A total of 32 patients were originally included in the study. Of these 5, did not undergo a baseline PET/CT scan and one patient experienced spontaneous symptom relief and, thus, did not undergo surgery leaving a total of 26 patients (16 males) with baseline PET/CT to be included in the analysis. They had a mean age of 49.7 years and a mean BMI of 26.3 (Table 1). Twenty-two patients underwent surgery within one year from onset of radicular leg pain, while 4 (15.4%) had a symptom duration of more than one year at the time of surgery. At baseline, patients reported a mean health-related quality of life as measured by the EuroQol-5D (EQ-5D) of 0.53 and a mean Oswestry Disability Index (ODI) of 42.9. Mean back Visual Analogue Scale (VAS) and leg VAS were 39.5 and 65.3 respectively (Table 1).

Table 1
Characteristics of patient population

| Variables | All (<i>n</i> = 26) |
|---|----------------------|
| Age, mean (SD) | 49.7 (7.35) |
| Males, <i>n</i> (%) | 16 (61.5) |
| BMI, mean (SD) | 26.3 (3.72) |
| Duration of leg pain > 1-year, <i>n</i> (%) | 4 (15.4) |
| EQ5D baseline, mean (SD) | 0.53 (0.21) |
| ODI baseline, mean (SD) | 42.9 (12.7) |
| VAS back-pain baseline, mean (SD) | 39.5 (26.2) |
| VAS leg-pain baseline, mean (SD) | 65.3 (20.6) |
| BMI: Body Mass Index, EQ5D: EuroQol-5D, ODI: Oswestry Disability Index, VAS: Verbal Analogue Scale. | |

Testing for cerebral diaschisis yielded the following total hemispheric glucose metabolism ratio (THGr) values for the entire material without any outliers: mean 0.96, median 0.98, range 0.89-1.00, i.e., values indicating normal conditions according to previous literature^{5,6}. Standardized uptake values (SUV) in left and right thalamus are displayed in Table 2.

Table 2
FDG-PET/CT measurements of the right and left thalami among included patients.

| | Right thalamus (<i>n</i> = 26) | Left thalamus (<i>n</i> = 26) |
|--|---------------------------------|--------------------------------|
| SUVmean, median (min;max) | 8.20 (6.1;13.6) | 8.20 (6.2;13.6) |
| cSUVmean, median (min;max) | 8.85 (6.5;14.7) | 9.00 (6.6;14.2) |
| SUV: Standardized Uptake Value, cSUV: Corrected Standardized Uptake Value. | | |

Of the 26 patients with baseline PET/CT scans, 25 reported unilateral radiating leg pain in conjunction with some degree of back pain. The side to which the pain was radiating, was registered using the baseline questionnaire and was used to test the hypothesis of lateralization of thalamic metabolism in conjunction with unilateral pain. One patient reported bilateral radicular leg pain and was therefore not included in these analyses. For each of the abovementioned SUV metrics, the hemisphere with the highest thalamic SUV measure (mean and partial volume corrected mean) was noted and compared to the side of radicular leg pain. Numbers were entered into a contingency table and results were evaluated. The SUVmean and cSUVmean showed lateralization towards the thalamus opposite to the registered pain side (Table 3). By Fisher's exact test, statistics showed significance for cSUVmean (*p*-value 0.027).

Table 3
Comparison of painful body side and increased FDG-PET/CT activity in the right and left thalamus.

| Increased PET activity in thalamus | Painful body side | | <i>p</i> -value |
|--|-------------------|---------|-----------------|
| | Right | Left | |
| SUVmean, <i>n</i> = 25 | | | |
| Right, <i>n</i> (%) | 4 (16%) | 9 (36%) | |
| Left, <i>n</i> (%) | 7 (28%) | 5 (20%) | 0,163 |
| cSUVmean, <i>n</i> = 25 | | | |
| Right, <i>n</i> (%) | 2 (8%) | 9 (36%) | |
| Left, <i>n</i> (%) | 9 (36%) | 5 (20%) | 0.027* |
| SUV: Standardized Uptake Value, cSUV: Corrected Standardized Uptake Value. | | | |

To investigate if the PET/CT scan metrics correlated with the clinical parameters reported by the patients, a mean thalamic glucose metabolism ratio (MTGr) was computed. The cSUVmean of the thalamus contralateral to the pain side was indexed to the ipsilateral thalamic metabolism, resulting in MTGr values, which – when above one – indicated the hypothesized relation between metabolism lateralization and pain side.

The computed MTGr was evaluated for correlations with patients' reported pain perception and subsequent clinical outcome measures. Correlation coefficients for baseline pain perception and self-reported quality of life were generally low ($\rho < 0.40$), and none reached statistical significance.

As only 18 of the 26 patients followed the hypothesized contingency table, a separate correlation analysis was run on these patients to see if that produced other correlation coefficients. The correlation between MTGr and EQ-5D showed a coefficient of -0.47 (p -value 0.048), but again, the remaining coefficients indicated weak correlations.

To test if lateralization of thalamic metabolism was associated with clinical outcome of surgical treatment, a Spearman's rank correlation test was set up between MTGr and the 1-year change scores of patients reported outcome measures. A correlation coefficient of -0.50 (p -value 0.068) was found between MTGr and change in VAS backpain. The remaining coefficients all indicated weak correlations ($\rho < 0.40$). If stratifying the patients to only include the ones mentioned earlier (fitting the hypothesis), the correlation with EQ-5D change score was 0.54, but statistically non-significant (p -value 0.167). The aforementioned moderate correlation with the change in VAS back pain became very weak ($\rho < 0.20$), however, the coefficient between MTGr and change in VAS leg pain rose to -0.51 (p -value 0.194).

Discussion

We found a statistically significant pattern of an increase in thalamic glucose metabolism contralateral to the painful body region. Furthermore, there was a moderate correlation between quality of life and the ratio of thalamic glucose metabolism in patients with increased metabolism contralateral to their painful body side. A similar slight, but statistically insignificant, correlation, was found with regard to change in VAS back and leg pain.

Only a very limited amount of literature exists on changes in cerebral glucose metabolism as a result of pain perception and, therefore, direct comparisons to previous published results were not an option. As there is no standard protocol for using PET/CT to quantify changes in brain metabolism due to painful stimuli, we chose to use the European Association of Nuclear Medicine procedure guidelines for tumor imaging in the acquisition of SUV metrics⁷. This was done to apply known methods for quantifying metabolism and to facilitate an easier reproduction of the techniques applied.

In order to analyze and quantify lateralization in the thalamus of each hemisphere we tested for and found no signs of general cerebral diaschisis as previously described by Segtnan et al.⁶. Both the median and range of the SUV metrics for the cerebral hemispheres were compared with previously reported findings of a median cerebral hemisphere ratio of 0.95, ranging between 0.65-1.00 in healthy individuals. The present findings with a median of 0.98, ranging 0.89-1.00 are clearly within what is considered normal and, thus, were an indication of absence of cerebral hemispheric diaschisis.

We hypothesized that unilateral pain would lead to an increased glucose metabolism of the contralateral thalamus as a result of the afferent synapse in the somatosensory pathway. The results in Table 3 show

the cSUVmean indicated a contralateral relationship between pain and increase in thalamic activity. The significance of this finding was a result of partial volume correction which, due to the limited spatial resolution of whole-body PET scanners, is necessary for proper quantification of tracer uptake in small structures as the thalamus⁸. The reason for using the ratio between the two hemispheres, as opposed to the nominal values, was to make the individual patients serve as their own controls to adjust for inter-scan differences, which might otherwise skew the results.

As far as we know, these findings are the first quantitative cerebral glucose metabolism results reported in surgical candidates with LDH. A previous study by Newberg et al. found significant asymmetry in thalamic blood flow using SPECT in patients with chronic pain syndrome⁴. Their observations indicated a significantly higher degree of lateralization in patients with pain compared to healthy controls. Despite being measures of cerebral blood flow and not metabolism, one would expect those two parameters to present some collinearity. Similar results were reported by Guillot et al., who found significantly increased thalamic activity in cats with osteoarthritis-associated pain⁹, whereas Iadarola et al., using ¹⁵O-water bolus PET, reported a decrease in contralateral thalamic blood flow in four patients with chronic post-traumatic neuropathic pain in one lower limb and one patient with post-herpetic facial neuralgia¹⁰. Decreases were maximally 15% compared to 8% higher uptake in two of our patients, 20% higher in five and 36% higher in the remaining 18 patients. As cause of the unexpected decreases, the authors suggested neurodegeneration known to accompany pathological increases in neural activity, excessive inhibition of thalamic activity to over-compensate for excessive excitatory nociceptive inputs, "learning" in that chronic pain may be transmitted with less activity within the thalamus as times go by, and uncoupling of blood flow from metabolism in the thalamus. The authors had no convincing arguments for any possibility. Nonetheless, it appears that decreased contralateral flow may be influenced by the duration of pain, which was $\geq 2-2\frac{1}{2}$ years in four of their five patients compared to less than a year in 22 of our 26 patients, so that "learning" might in fact play a certain role. However, in view of the extreme versatility of measured regional cerebral flow [19, 20], vast heterogeneity among chronic pain patients, and the authors' use of parametric instead of nonparametric statistics in such a small material make it difficult to accept these results at face value.

Correlations between quantitative measurements of glucose metabolism in the thalamus and clinical measures (VAS, disability and quality of life) were found to be moderate at best, and only when excluding patients not conforming with the abovementioned hypothesis of increased activity contralateral to the symptomatic side, did we find statistically significant correlations. This may lead to speculations on whether a correlation actually exists, as the coefficients were only moderate, and scatterplots of the observations did not indicate a convincing pattern (data not shown). The correlation with EQ-5D were the most consistent and indicated a worse quality of life at baseline when a higher ratio between the two thalami was measured. Likewise, a higher change in EQ-5D was observed at 1-year when the ratio had increased. This harmonizes well with the hypothesis that increased lateralization is indicative of a chronic pain condition and subsequently decreased physical and psychological well-being. When

correlating the glucose metabolism ratio with pain perception measured by VAS leg- and back pain, the results were more diverse, and, therefore, less likely to be consistent in a larger cohort.

We acknowledge that our relatively small cohort is a limitation, as any observation will need to produce a relatively uniform and large signal for this to come out significant. This also means that any outliers will skew the results towards a type II error. A further limitation of unknown proportion is the patients' use of pain medication, which was not recorded. Despite being asked not to take pain medication in five times the half-life of each drug before the PET/CT scan, the actual compliance with this instruction was unknown. Furthermore, the described method of quantifying glucose metabolism was only partly standardized and, therefore, probably somewhat observer dependent.

The current study sustains the hypothesis that unilateral pain of LDH patient is associated with an increase in the metabolism of the thalamus of the contralateral hemisphere in line with the suggestion that thalamus may operate as some sort of a "relay station" in pain perception. Whether there is a nominal relation between metabolism ratio and subjective pain perception is unclear, however, our data seem to suggest that quality of life is negatively affected by a higher degree of thalamic imbalance. Further research is needed, preferably using high resolution scanners and MRI segmentation, to confirm if our preliminary findings hold water and can serve as a basis for optimized post-surgery pain management in LDH.

Materials And Methods

Patient population and study course

Between September 2014 and September 2015 all patients aged 40–65 years, who after referral were found eligible for surgery at a major Danish degenerative spine center due to LDH were asked to participate. Exclusion criteria were pregnancy, malignant disease, prior radiation treatment, spine surgery or spinal fractures, psychiatric disorders and chronic pain conditions not attributable to LDH, i.e., generalized connective tissue disorders, chronic regional pain syndrome, etc. Patients who gave consent to participation underwent an FDG-PET/CT scan no more than two weeks prior to surgery. Demographics and data on pain, physical function and health were collected using questionnaires from the Danish national surgical spine database (DaneSpine)¹¹. All participants received the standard care of the spine center, and surgery was performed by a senior consultant using ordinary discectomy or a minimally invasive surgical approach.

PET/CT imaging

Patients were asked to refrain from pain medication 36 hours (5 x the half-life of relevant drugs) prior to their PET/CT scan and were kept fasting for at least 6 hours before their scan. They were placed supine on the tomography bed in a quiet room with dim lighting, and their head was immobilized with a dedicated headrest. Following 10 minutes of rest, FDG (4 MBq/kg body weight) was administered intravenously. Images were obtained using an acquisition protocol with 47 slices (3.3 mm) in each frame

on a General Electric Discovery PET/CT 690 or 710 scanner. A complete PET/CT scan from top of the head to sacrum was performed, and data from 60–90 min. acquisition was summed and used for analyses. All scans were performed at the Department of Nuclear Medicine, Odense University Hospital, in accordance with local standard operating procedures.

PET images were segmented and analyzed using ROVER software (v2.1 ABX, Radeberg, Germany). Proper head alignment was examined prior to defining region of interest (ROI). Head tilt was corrected manually on the CT using a global pixel shift, thereby not altering pixel size or values. After fusing the PET/CT using DICOM information, a rigid correction for head movement on the PET image was done in order to ensure proper PET/CT overlap. Subsequently, an ovoid ROI was defined by the observer on a scan-to-scan basis to best fit the thalamus structure in one hemisphere. This mask was then duplicated in exact size and shape and applied to circumscribe the contralateral thalamus.

A lower fixed threshold of 41% of the peak SUV was applied to exclude cerebrospinal fluid activity and spillover from other surrounding structures. For each of the segmented regions, ROVER calculated the volume of the ROI together with the following SUV metrics: mean, and mean partial volume corrected, which were designated SUVmean and cSUVmean, respectively. Prior to further analysis of PET/CT data, all patients were tested for hemispheric diaschisis in order to eliminate any generalized cerebral metabolic lateralization. In brief, diaschisis is the finding of a remote functional disturbance in a region connectively related to a focal brain damage area. The presence of diaschisis is searched for by calculating the THGr as described by Segtnan et al. ⁶.

Collection of patient-reported outcome measures

All patient-reported outcome measures were retrieved from the Danish national surgical spine database (DaneSpine) at baseline and one-year follow-up ¹¹. Data was collected as previously described ¹². Variables collected were entirely patient-reported, including age, sex, height, weight, duration of back and leg pain prior to surgery, back and leg pain on a 0-100 VAS scale ¹³, EQ-5D ^{14,15}, and spine-related disability as measured by ODI^{16,17}.

Ethics

The current study was performed as an experimental prospective cohort study in accordance with the STROBE guidelines ¹⁸. Patients were given written and oral information on the purpose, nature and implications of study participation. Information and inclusion of participants was conducted in accordance with the guidelines of The Health Research Ethics Committee System in Denmark, by which the study protocol was approved prior to commencing the study (S-20140052).

Statistical analysis

All statistical analyses were performed with STATA 16 (StataCorp., College Station, TX). As the number of observations were low, a p-value of < 0.05 was considered significant. Categorical data are presented by frequencies and related percentages; continuous data are displayed by means of descriptive statistics

(mean/median, range, number of observations). Categorical variables and contingency tables were analyzed for significant difference using Fisher's exact test. Continuous variables were analyzed for correlations with PET/CT parameters using Spearman's rank correlation coefficient test. Correlation coefficients of < 0.40 were considered weak.

Declarations

Funding

This work was supported in part by 1-year PhD scholarship to CCS from the Faculty of Health Sciences, University of Southern Denmark, from the Lillebaelt Hospital Research Council, and the IMK Almene Fond.

Competing interests

The authors declare they have no conflict of interest.

Authors' contributions

CCS, MØA, AA, and PFHC contributed to conception and design, drafted or revised the manuscript. Together with CCS, CC and RP made the data analysis twice. MK collaborated with regard to methodology and interpretation. AN made contribution to interpretation of the data and revised the manuscript. All authors approved the submitted version of the manuscript and agreed to be accountable for all aspects of the work.

References

1. Helmerhorst, G. T., Teunis, T., Janssen, S. J. & Ring, D. An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada: is Europe next? *Bone Joint J*, **99-B**, 856–864 <https://doi.org/10.1302/0301-620X.99B7.BJJ-2016-1350.R1> (2017).
2. Kalkman, G. A., Kramers, C., van Dongen, R. T., van den Brink, W. & Schellekens, A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. *Lancet Public Health*, **4**, e498–e505 [https://doi.org/10.1016/S2468-2667\(19\)30128-8](https://doi.org/10.1016/S2468-2667(19)30128-8) (2019).
3. McBain, R., Rose, A. J. & LaRochelle, M. R. The U.S. opioid epidemic: One disease, diverging tales. *Prev. Med*, **112**, 176–178 <https://doi.org/10.1016/j.ypmed.2018.04.023> (2018).
4. Newberg, A. B. *et al.* Cerebral blood flow effects of pain and acupuncture: a preliminary single-photon emission computed tomography imaging study. *J. Neuroimaging*, **15**, 43–49 <https://doi.org/10.1177/1051228404271005> (2005).

5. Segtnan, E. A. *et al.* Prognostic Implications of Total Hemispheric Glucose Metabolism Ratio in Cerebrocerebellar Diaschisis. *J. Nucl. Med*, **58**, 768–773 <https://doi.org/10.2967/jnumed.116.180398> (2017).
6. Segtnan, E. A. *et al.* Diagnostic manifestations of total hemispheric glucose metabolism ratio in neuronal network diaschisis: diagnostic implications in Alzheimer's disease and mild cognitive impairment. *Eur. J. Nucl. Med. Mol. Imaging*, **46**, 1164–1174 <https://doi.org/10.1007/s00259-018-4248-0> (2019).
7. Boellaard, R. *et al.* FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur. J. Nucl. Med. Mol. Imaging*, **42**, 328–354 <https://doi.org/10.1007/s00259-014-2961-x> (2015).
8. Alavi, A., Werner, T. J., Hoiland-Carlsen, P. F. & Zaidi, H. Correction for Partial Volume Effect Is a Must, Not a Luxury, to Fully Exploit the Potential of Quantitative PET Imaging in Clinical Oncology. *Mol. Imaging Biol*, **20**, 1–3 <https://doi.org/10.1007/s11307-017-1146-y> (2018).
9. Guillot, M. *et al.* [(18)F]-fluorodeoxyglucose positron emission tomography of the cat brain: A feasibility study to investigate osteoarthritis-associated pain. *Vet. J*, **204**, 299–303 <https://doi.org/10.1016/j.tvjl.2015.03.023> (2015).
10. Iadarola, M. J. *et al.* Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain., **63**, 55–64 [https://doi.org/10.1016/0304-3959\(95\)00015-k](https://doi.org/10.1016/0304-3959(95)00015-k) (1995).
11. Hojmark, K., Stottrup, C., Carreon, L. & Andersen, M. O. Patient-reported outcome measures unbiased by loss of follow-up. Single-center study based on DaneSpine, the Danish spine surgery registry. *Eur. Spine J*, **25**, 282–286 <https://doi.org/10.1007/s00586-015-4127-3> (2016).
12. Stottrup, C. C., Andresen, A. K., Carreon, L. & Andersen, M. O. Increasing reoperation rates and inferior outcome with prolonged symptom duration in lumbar disc herniation surgery - a prospective cohort study. *Spine J*, <https://doi.org/10.1016/j.spinee.2019.04.001> (2019).
13. Williamson, A. & Hoggart, B. Pain: a review of three commonly used pain rating scales. *J. Clin. Nurs*, **14**, 798–804 <https://doi.org/10.1111/j.1365-2702.2005.01121.x> (2005).
14. EuroQol, G. EuroQol—a new facility for the measurement of health-related quality of life., **16**, 199–208 (1990).
15. Sorensen, J., Davidsen, M., Gudex, C., Pedersen, K. M. & Bronnum-Hansen, H. Danish EQ-5D population norms. *Scand J Public Health*, **37**, 467–474 <https://doi.org/10.1177/1403494809105286> (2009).
16. Fairbank, J. C., Couper, J. & Davies, J. B. & O'Brien, J. P. The Oswestry low back pain disability questionnaire. *Physiotherapy*, **66**, 271–273 (1980).
17. Lauridsen, H. H., Hartvigsen, J., Manniche, C., Korsholm, L. & Grunnet-Nilsson, N. Danish version of the Oswestry Disability Index for patients with low back pain. Part 1: Cross-cultural adaptation, reliability and validity in two different populations. *Eur. Spine J*, **15**, 1705–1716 <https://doi.org/10.1007/s00586-006-0117-9> (2006).

18. von Elm, E. *et al.* [The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies]. *Internist (Berl.)*, **49**, 688–693 <https://doi.org/10.1007/s00108-008-2138-4> (2008).