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Does size matter? Brain structure in low back pain: protocol for a systematic review and ALE meta-analysis of morphometric data

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Review question(s)

What are the differences in brain gray matter volume and density in human adults with low back pain, compared to controls?

What are the differences in brain white matter structure in human adults with low back pain, compared to controls?

Which of the following clinical and methodological characteristics explain the observed structural differences: pain intensity, duration of low back pain, type of low back pain, depression and control for medication use in the study?

We will functionally characterise the brain areas that are identified as structurally different in people with low back pain.

Searches

The following electronic databases will be searched: MEDLINE and EMBASE via Ovid, CINAHL, PsycINFO and BrainMap via Sleuth (BrainMap, University of Texas) (Fox & Lancaster, 2002; Fox et al., 2005; Laird, Lancaster, & Fox, 2005). The reference lists of all included studies or reviews that are identified during the search will be scrutinised for additional resources. Experts in the field will be contacted to see if they are aware of any other published material.

Only peer-reviewed journal articles will be considered. No other restrictions will occur

References:

Fox, P. T., & Lancaster, J. L. (2002). Opinion: Mapping context and content: the BrainMap model. *Nature Reviews. Neuroscience*, 3(4), 319–321. <http://doi.org/10.1038/nrn789>

Fox, P. T., Laird, A. R., Fox, S. P., Fox, P. M., Uecker, A. M., Crank, M., ... Lancaster, J. L. (2005). BrainMap taxonomy of experimental design: Description and evaluation. *Human Brain Mapping*, 25(1), 185–198. <http://doi.org/10.1002/hbm.20141>

Laird, A. R., Lancaster, J. L., & Fox, P. T. (2005). BrainMap: The social evolution of a functional neuroimaging database. *Neuroinformatics*, 3, 65–78.

Types of study to be included

There is no restriction on the design of studies to be included in the review.

Where studies include participants with LBP amongst other diagnostic groups, we will only include studies where LBP specific results are available. Where the same sample has been used in multiple papers, we will only include more than the original paper if each subsequent paper is a different form of analysis

Condition or domain being studied

Low back pain (LBP) is the leading cause of years lived with disability worldwide (Collaborators, 2015). Most low back pain resolves quickly, however a moderate proportion of people will develop persistent symptoms (da C. Menezes Costa et al., 2012; Henschke et al., 2008; Wynne-Jones et al., 2014). Those people for whom pain persists use a disproportionate amount of healthcare compared to people with short term LBP or matched controls (Becker, 2010; Hang 2012) and do not seem to get better (da C. Menezes Costa et al., 2012) in spite of what we do (Artus et al., 2010). The expansive costs to individual and society, poor treatment effectiveness and the plateau in recovery provide great incentive to understanding more about the problem.

References:

Artus, M., van der Windt, D. A., Jordan, K. P., & Hay, E. M. (2010). Low back pain symptoms show a similar pattern of improvement following a wide range of primary care treatments: a systematic review of randomized clinical trials. *Rheumatology (Oxford, England)*, 49(12), 2346–56. <http://doi.org/10.1093/rheumatology/keq245>

Becker, A., Held, H., Redaelli, M., Strauch, K., Chenot, J. F., Leonhardt, C., ... Donner-Banzhoff, N. (2010). Low back pain in primary care: costs of care and prediction of future health care utilization. *Spine*, 35(18), 1714–1720. <http://doi.org/10.1097/BRS.0b013e3181cd656f>

Collaborators, G. S. 2013. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*. [http://doi.org/10.1016/S0140-6736\(15\)60692-4](http://doi.org/10.1016/S0140-6736(15)60692-4)

Da C. Menezes Costa, L., Maher, C. G., Hancock, M. J., McAuley, J. H., Herbert, R. D., & Costa, L. O. P. (2012). The prognosis of acute and persistent low-back pain: a meta-analysis. *CMAJ*, 184(11), 1229–1230. <http://doi.org/10.1503/cmaj.111271>

Henschke, N., Maher, C. G., Refshauge, K. M., Herbert, R. D., Cumming, R. G., Bleasel, J., ... McAuley, J. H. (2008). Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *BMJ (Clinical Research Ed.)*, 337, a171. <http://doi.org/10.1136/bmj.a171>

Hong, J., Reed, C., Novick, D., & Happich, M. (2012). Costs Associated With Treatment of Chronic Low Back Pain. *Spine*, 38(1), 1. <http://doi.org/10.1097/BRS.0b013e318276450f>

Wynne-Jones, G., Cowen, J., Jordan, J. L., Uthman, O., Main, C. J., Glozier, N., & van der Windt, D. (2014). Absence from work and return to work in people with back pain: a systematic review and meta-analysis. *Occupational and Environmental Medicine*, 71(6), 448–56. <http://doi.org/10.1136/oemed-2013-101571>

Participants/ population

Human adults with low back pain of any duration, defined as site of greatest pain between the 12th rib and gluteal fold, with or without associated leg pain. Studies that involve people with non-specific low back pain or sciatica will be considered for inclusion.

Studies will be excluded if they contain subjects with low back pain caused by pathological entities such as infection, neoplasm, metastasis, osteoporosis, inflammatory disease or fractures

Intervention(s), exposure(s)

All studies that have used structural brain imaging techniques to examine human brain morphometry will be considered. Studies that examine spinal cord or peripheral nerve structure will be excluded.

Only whole brain analyses will be considered for inclusion in the meta-analyses. Studies making any form of a priori restrictions on their analysis will be included in the review but excluded from meta-analysis.

Comparator(s)/ control

Studies must have a healthy comparison group, matched for age and gender.

Outcome(s)

Primary outcomes

The primary outcomes are the region specific difference in ...

1. gray matter volume
2. gray matter density
3. white matter structure

...between people with and without low back pain

Coordinate data that are collected in Talairach space will be converted to MNI space using the `icbm2tal` function (Laird et al., 2010; Lancaster et al., 2007).

Analyses will be stratified according to gray/white matter type, type of outcome value (mean diffusivity, fractional anisotropy, gray matter volume (modulated images) or density (unmodulated images)) and direction of effect (e.g. increase vs decrease in outcome value).

References:

Laird, A. R., Robinson, J. L., McMillan, K. M., Tordesillas-Gutiérrez, D., Moran, S. T., Gonzales, S. M., ... Lancaster, J. L. (2010). Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. *NeuroImage*, 51(2), 677–83. <http://doi.org/10.1016/j.neuroimage.2010.02.048>

Lancaster, J. L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., ... Fox, P. T. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping*, 28(11), 1194–205. <http://doi.org/10.1002/hbm.20345>

Secondary outcomes

Secondary outcomes are the within group influence of pain intensity and duration of low back pain on each of: gray matter volume, gray matter density and white matter structure between people with and without low back pain.

Risk of bias (quality) assessment

Included studies

A customised risk of bias tool will be developed for this review. The tool will be based on the Newcastle-Ottawa Scale (Wells et al., 2014), which has received support from the Cochrane collaboration as a quality assessment tool for observational studies. The tool will also include several supplementary items from a tool previously developed by our group (Di Pietro et al., 2013) that we have deemed important to the conduct of neuroimaging studies. The tool will examine both the quality of methods used and the standard of reporting in the paper.

Meta-bias

A jack-knife analysis (Radua & Mataix-Cols, 2009) will be conducted of the ALE results post meta-analysis to examine whether specific clusters are being driven by a low number of studies and should thus be interpreted with caution (Cauda et al., 2014). Jackknife analysis gives an idea of the reproducibility of the finding at each cluster by testing iterations with one study excluded each time. If a cluster remains significant in most or all of the iterations, it is likely to be a highly replicable result (Radua & Mataix-Cols, 2009).

References:

Cauda, F., Palermo, S., Costa, T., Torta, R., Duca, S., Vercelli, U., ... Torta, D. M. E. (2014). Gray matter alterations in chronic pain: A network-oriented meta-analytic approach. *NeuroImage: Clinical*, 4, 676–686. <http://doi.org/10.1016/j.nicl.2014.04.007>

Di Pietro, F., McAuley, J. H., Parkitny, L., Lotze, M., Wand, B. M., Moseley, G. L., & Stanton, T. R. (2013). Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *The Journal of Pain?: Official Journal of the American Pain Society*, 14(10), 1001–18.
<http://doi.org/10.1016/j.jpain.2013.04.001>

Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry*, 195(5), 393–402. <http://doi.org/10.1192/bjp.bp.108.055046>

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale (NOS). Retrieved from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Strategy for data synthesis

It is the intention that all included studies will be subjected to anatomic likelihood estimation (ALE) meta-analysis. Studies that are not eligible for meta-analysis (missing data, a priori restrictions on analysis) will be reported in narrative form. Treatment cohort studies will only have baseline (pre-treatment) data included in the meta-analyses.

We will use custom MATLAB tools to conduct the meta-analyses. We will present the results in MNI coordinates, with cluster sizes and as images.

Analysis of subgroups or subsets

We aim to perform additional subgroup analyses to explore the influence of pain intensity, type of pain-state (nociceptive, neuropathic and mixed aetiology), duration of low back pain (acute – pain < 6 weeks, subacute – pain 6-12 weeks, chronic – pain > 12 weeks), level of depression and control for medication use on brain structure differences. Where it is not possible to subgroup studies in the manner specified a priori, a sensitivity analysis will be considered to determine the effect on the meta-analysis of pooling studies that are heterogeneous. Sensitivity analyses will also be considered to explore the effects on the meta-analyses results of factors that were not identified a priori

Dissemination plans

The results of the review will be published in peer-reviewed academic journals and submitted for presentation at conferences

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Anticipated completion date

01 September 2016

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Conflicts of interest

None known

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Brain; Brain Mapping; Humans; Low Back Pain

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Ongoing

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Stage of review at time of this submission

	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

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