Examining the Psychosocial Burden of Pain on Functional and Morphological Brain Signatures

C Tanguay-Sabourin[1], M G Fillingim[1], G V Guglietti[2], M Roy[3], M O Martel[2], L Diatchenko[2], E Vachon-Presseau[2]

[1] Integrated Program in Neuroscience, McGill University, Canada [2] Faculty of Dentistry & Department of Anesthesia, McGill University, Canada. [3] Department of Psychology, McGill University, Canada.

Contact Information: c.tanguaysabourin@gmail.com

Introduction

Pain is a global burden given its high prevalence and pain-related comorbidities[1].

Recent efforts have been done on identifying clinically relevant signatures for chronic pain in the brain[2].

Separating the impact of chronic pain from the impact of associated physical and mental health remains a major challenge.

Objective

Examine a psychosocial burden of pain from health determinants (socio-demographics, mental health and physical health) and its association with functional and morphological brain signatures.

Methods

Population: A multivariate psychosocial burden index was derived in a large independent population (n = 450,000) from the United-Kingdom Population (40 years and older, 54% women)[1] and is examined here on an independent cohort who underwent Magnetic Resonance Imaging (see **Poster #1038655**).

Grey-Matter: Partial least square was used to identify the single most coherent mode of covariance between self-reported number of pain sites and grey-matter morphology, using the UK Biobank grey-matter atlas [3].

Functional Connectivity: Time series were extracted using Brainnetome atlas (279-regions) and dynamic conditional correlation was measured and averaged. The top 5% of connectivity links were selected and a Tonic Pain Signature [4] response was computed.

Nuisance covariates: Features and confounds were normalized. Then, age, sex, imaging site, head size, position in the scanner were regressed out from our features (including the head motion for functional data and total grey-matter for structural data).

Randomization (permutation) test: To ensure the robustness of small associations, we perform our association to 10,000 randomly generated null models.

Results

Fig. 1. *(Right)* Pain Phenotype and Burden associated with the number of self-reported pain sites. A. Major pain sites assessed in the UK Biobank. **B.** Association from the burden score (generated in independent population; see *Poster #1038655*) with the number of self-reported pain sites. **C.** Explained variance across each of the ten categories, all statistically significant ($p < 1 \times 10^{-15}$).

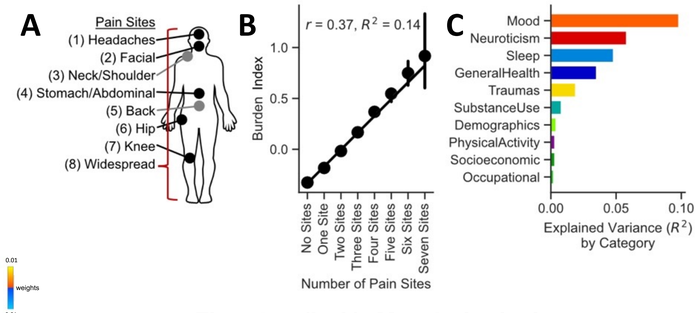


Fig. 2. *(Left)* Morphological grey-matter density pattern representation and validation associated with number of self-reported pain sites. A. Grey-Matter atlas (139 regions) defined in the UK Biobank using FMRIB's Automated Segmentation Tool (FAST).
B. Pattern representation across lateral/medial wall and brain stem and cerebellum after controlling for total grey-matter volume.
C. & D. Deriving the morphological grey-matter density pattern in a training dataset associated with multisite pain. C. Association with number of pain sites (*above*) and permutation test (*below*). **D.** Association with the burden index and permutation test. **E. & F. Validation of the pattern in an independent group dataset.** Test of the difference between two dependent correlations revealed that the Morphological Grey-Matter Pattern to be more associated with the burden index than the number of pain sites ($z = 5.3$, $p < 1 \times 10^{-5}$).

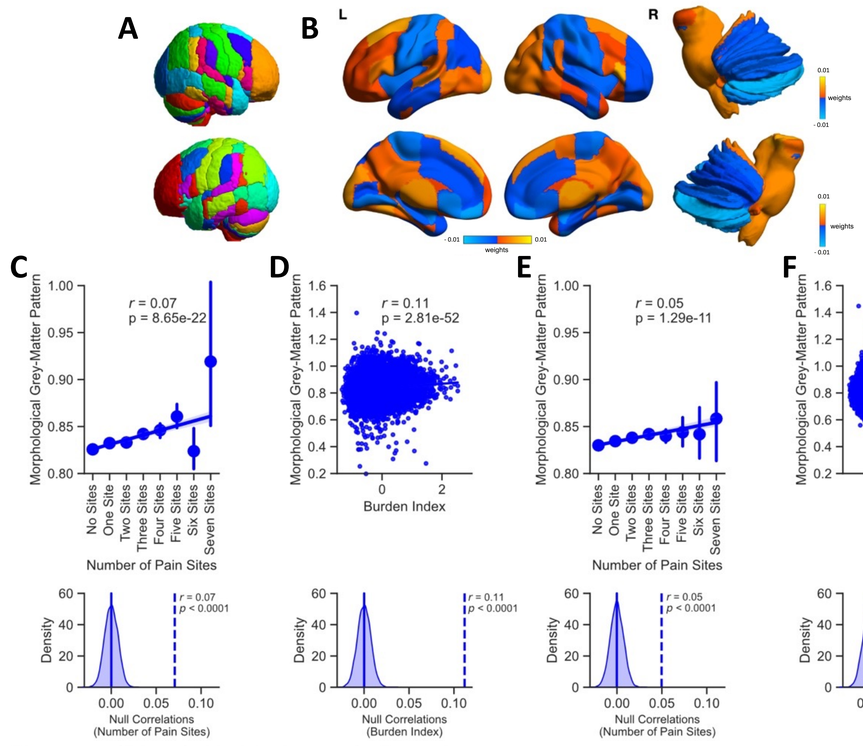
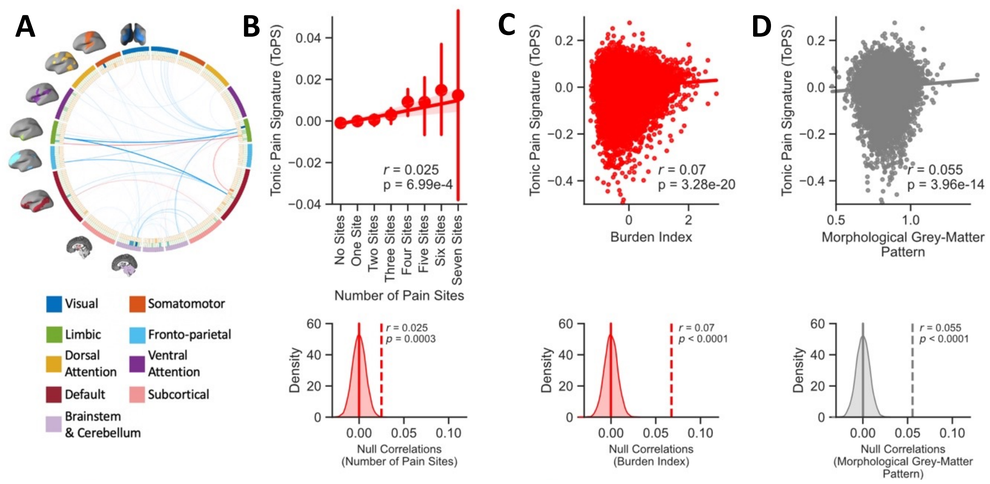


Fig. 3. *(Right)* Validation of Functional Tonic Pain Signature (ToPS) of experimental and clinical pain. A. ToPS[2] visualization (top 5% connectivity links; positive links in red and negative links in blue) across nine large-scale brain networks.
B & C. Assessing an *a-priori* pain signature in our validation dataset.
B. Association of the ToPS with the number of self-reported pain sites (*above*) and permutation test (*below*).
C. Association of the ToPS with the burden index and permutation. The ToPS also appeared to be more associated with the burden index than the number of pain sites ($z = 5.1$, $p < 1 \times 10^{-5}$).
D. Association between the Tonic Pain Signature and the Morphological Grey-Matter Pattern and permutation test.



Discussion

1) We validate a multivariate burden index associated with the number of self-reported pain sites in an independent cohort (see **Poster #1038655**)
2) Following the split of this cohort, we derive a multivariate morphological grey-matter density (GMD) pattern associated with multisite pain. This signature was characterized by decreased GMD in the somatosensory and medial wall of the frontal cortex with increased GMD in lateral left-frontal cortex and brainstem.
3) We validate a pre-defined experimental signature of tonic pain in our test data, characterized by limbic-default-frontal networks as major weights in top 5% connectivity.
4) The morphological grey-matter pattern was also associated with the tonic pain signature.
5) Both brain function and morphology were more closely linked to our burden index of pain than the pain phenotype our burden was derived from.

References

1. Rice, Smith, & Blythe (2016). Pain and the global burden of disease. *Pain.*
2. Davis, et al. (2017). Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nature Reviews Neurology.*
3. Miller, et al. (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neuroscience.*
4. Lee, et al. (2020). A neuroimaging biomarker for sustained experimental and clinical pain. *Nature Medicine.*

Acknowledgements

HEALTHY BRAINS HEALTHY LIVES
McGill Faculty of Medicine and Health Sciences