Brain structure differences in chronic pain are influenced by genetic differences

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Background

- **Clinical studies of chronic pain** using structural magnetic resonance imaging (MRI) show **reduced grey matter** (GM) across a number of brain regions
- It is not known whether these associations may be due to underlying genetic differences

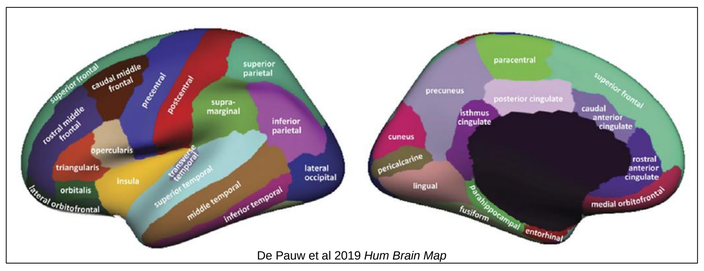
Research Questions

Can associations between chronic pain and brain morphology be explained through shared underlying genetics?

Do associations between chronic pain and brain morphology reflect causal relationships?

Method

- **Identify brain regions** with decreased morphology in chronic pain:
  → Prefrontal cortex, cingulate cortex, insula, thalamus, superior temporal gyrus



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- **Genome wide association studies (Fig. 1, Table 1)**:
  → Regional chronic pain conditions
  N = 196,963 cases, N = 239,125 controls

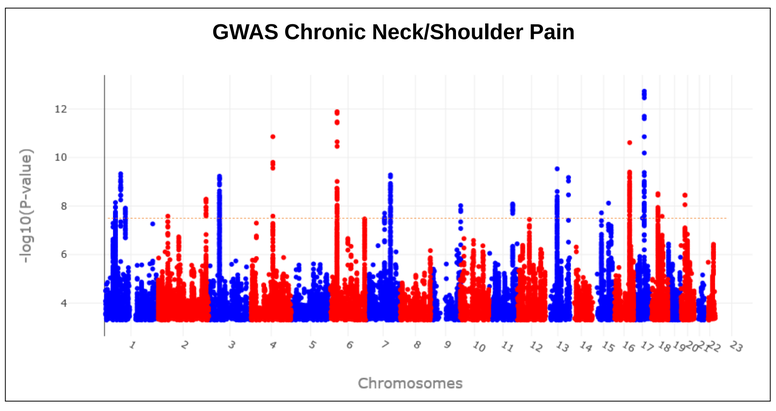

Figure 1 Example genome wide association study (GWAS) for chronic neck/shoulder pain. Each dot represents a single nucleotide polymorphism (i.e., genetic variant). Red line denotes significance threshold (p < 5.00E-08). Full GWAS details for each chronic pain type available at https://view.genoma.io

Pain site	Total
Any site	196,963
Widespread	6,063
Back	79,089
Face	4,037
Headache	39,283
Hip	41,677
Knee	77,996
Neck/shoulder	72,216
Abdominal	21,285
Controls	239,125

Table 1 Numbers of people in regional chronic pain and control groups

Method cont.

→ Structural MRI traits (publicly available)
N = 19,629–34,000
Cortical thickness, regional volume, subcortical volume

- Bivariate linkage disequilibrium-score regression to determine the **genetic correlations** (*rG*)
  → Quantifies shared underlying genetics
- Latent causal variable analysis and **genetic causal proportion** (GCP)
  → Quantifies evidence for causation
- False discovery rate < 5%

Results

- **Ten (of 369) significant negative genetic correlations (*rG*) observed at insula, posterior cingulate & pars triangularis** between MRI traits & chronic pain type (hip, neck/shoulder, abdominal, widespread pain, pain at any site) (Fig. 2)
  → Indicates that genetic variants associated with chronic pain are also associated with reduced regional brain GM morphology

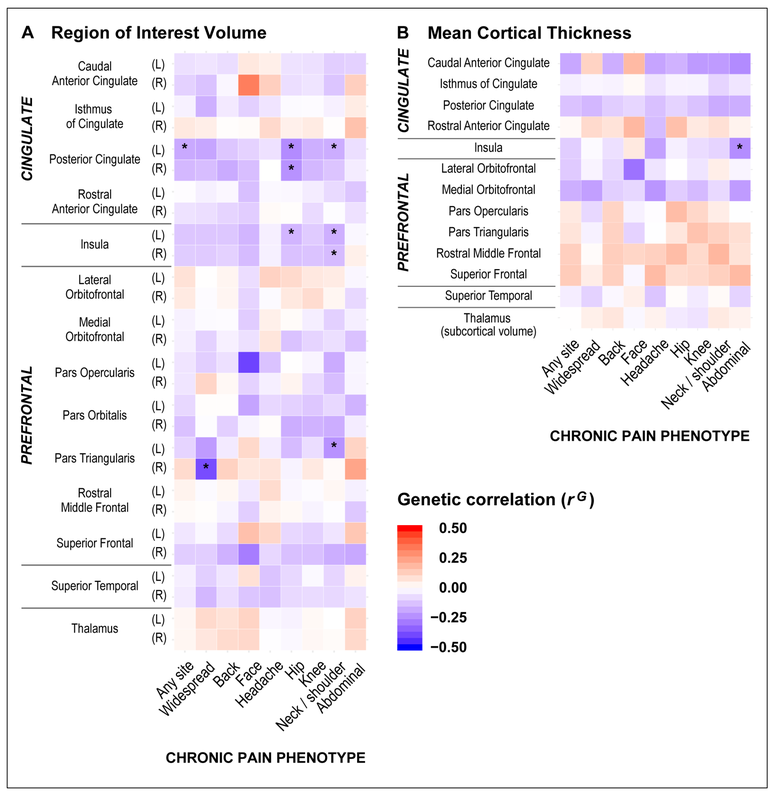

Figure 2 Heatmaps for genetic correlations (*rG*) between the chronic pain phenotypes and MRI traits. (A) Region of interest volume and (B) mean cortical thickness (or subcortical volume as applicable). Asterisk denotes significant *rG* at 5% false discovery rate. Direction of correlation is shown by heatmap colours (i.e., red denotes positive *rG* and blue denotes negative *rG*), with darker shading indicating stronger genetic associations

Results cont.

- **One significant genetic causal relationship** was found (Table 2)
  → Genes underlying reduced insula cortical thickness *causally contribute* to increased risk of chronic abdominal pain (*rG* [S.E.] = -0.25 [0.08], p = 1.06E-03; GCP [S.E.] = -0.69 [0.20], p = 4.96E-04)

Chronic pain	Brain region	MRI trait	*rG* (S.E.) p-value	GCP (S.E.) p-value
Hip pain	Left posterior cingulate	GMV	-0.25 (0.07) 2.08E-04	0.22 (0.48) 0.64
	Right posterior cingulate	GMV	-0.24 (0.07) 3.19E-04	0.43 (0.35) 0.21
	Left insula	GMV	-0.16 (0.06) 4.17E-03	0.41 (0.37) 0.27
Neck / shoulder pain	Left insula	GMV	-0.17 (0.05) 6.43E-04	-0.01 (0.30) 0.96
	Right insula	GMV	-0.15 (0.05) 1.41E-03	-0.07 (0.45) 0.88
	Left posterior cingulate	GMV	-0.17 (0.06) 2.09E-03	0.00 (0.42) >0.99
	Left pars triangularis	GMV	-0.24 (0.08) 3.50E-03	0.05 (0.37) 0.90
Abdominal pain	Mean insula (left & right)	Cortical thickness	-0.25 (0.08) 1.06E-03	-0.69 (0.20) 4.96E-04
Widespread pain	Right pars triangularis	GMV	-0.39 (0.12) 1.57E-03	-0.08 (0.21) 0.72
Pain at any site	Left posterior cingulate	GMV	-0.18 (0.05) 4.10E-04	0.01 (0.58) 0.99

GCP — genetic causal proportion, GMV — grey matter volume, MRI — magnetic resonance imaging, rG — genetic correlation, S.E. — standard error

Table 2 Grey matter (GM) morphology traits with significant genetic correlation (*rG*; FDR < 5%) with chronic pain. A negative genetic correlation indicates the chronic pain condition is associated with lower values of the GM trait. A positive genetic correlation indicates the chronic pain condition is associated with higher values of the GM trait. Genetic causal proportion (GCP) indicates the likelihood of chronic pain affecting a trait (+ve values) or the trait affecting chronic pain (-ve values). GCP is significant (FDR < 5%) for mean insula cortical thickness in chronic abdominal pain, which suggests the genes underlying reduced insula cortical thickness causally contribute to an increased risk of chronic abdominal pain. For the other genetic correlations with non-significant GCP, reduced regional GM volume was associated with the chronic pain phenotypes but without evidence of a causal relationship between the traits

Conclusions

- **Structural brain differences in chronic pain conditions can be explained (in part) by shared genetic factors**:
  → Insula, posterior cingulate & pars triangularis
  → Neck/shoulder, hip, abdominal, widespread pain & pain at any site
  → Convergent evidence corroborating clinical phenotypic studies
- **Causal relationship demonstrated** between reduced mean insula cortical thickness and chronic abdominal pain

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