

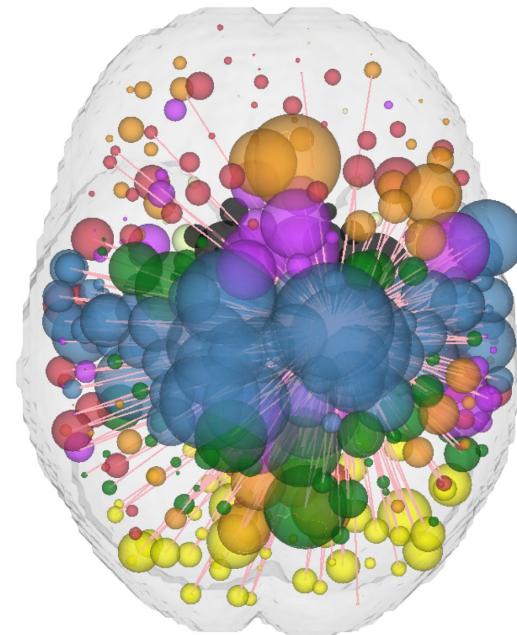


Neural Contributions to Sexual Pain

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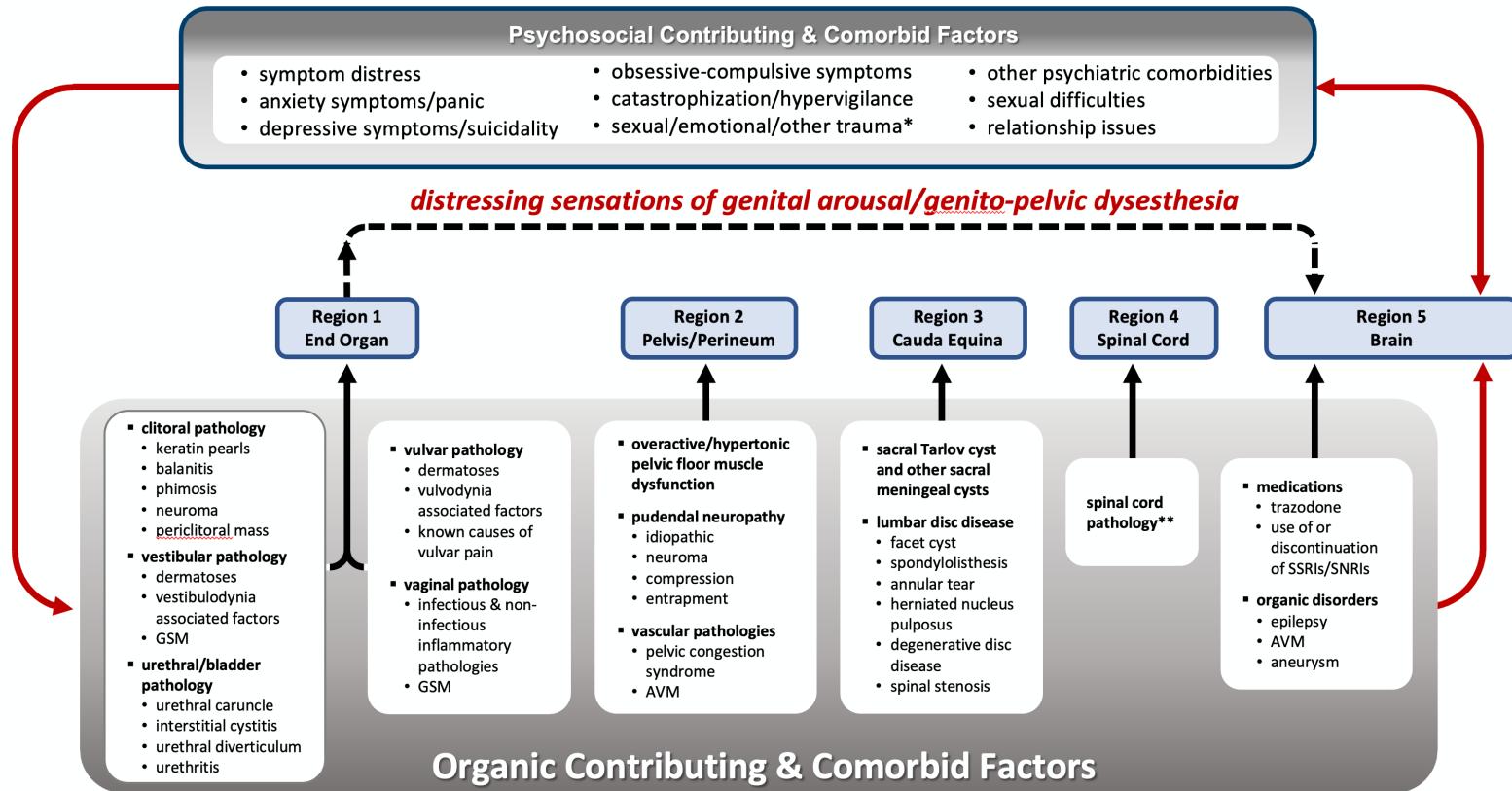
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No disclosures

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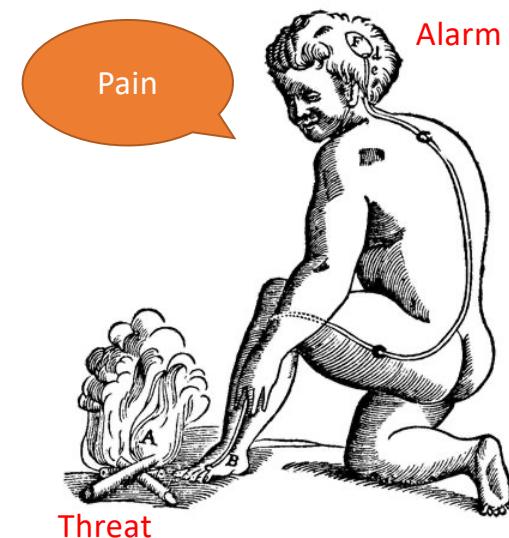
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Why suspect the central nervous system (CNS)?



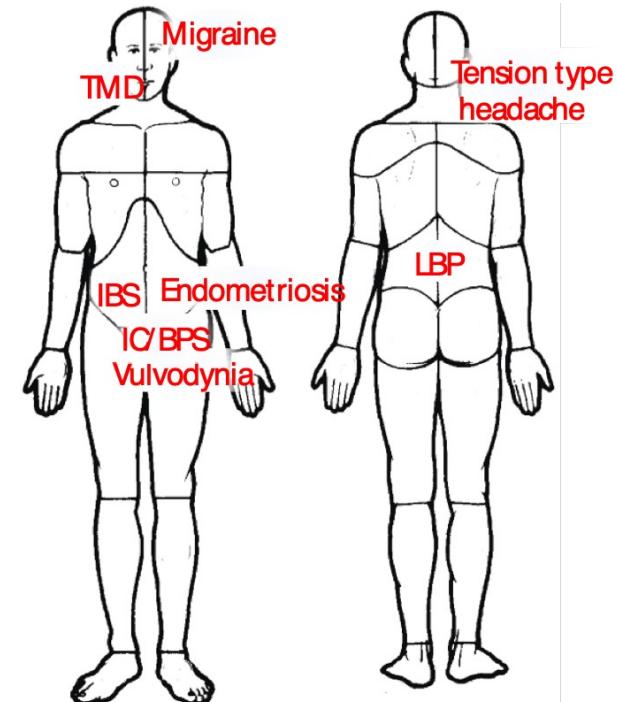
- When would removing the peripheral threat have less than the desired effect?
 - What if pain were distributed across the body?
 - What if CNS dysfunction predicated pain onset?
 - What if CNS structure predicted surgical response?
- How might you improve outcomes in at-risk individuals?



Chronic overlapping pain conditions (COPCs)



- “Coexisting pain conditions, ... as recognized by National Institutes of Health ... include, but should not be limited to, temporomandibular disorder (TMD), fibromyalgia (FM), irritable bowel syndrome (IBS), vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic lower back pain.”¹
- Already recognized to be more challenging clinically²⁻⁴
- Hypothesized indicator of central pain amplification⁵⁻⁶



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1. Maxiner et al., 2016
2. Brummett CM, et al. 2013
3. Brummett CM, et al., 2015
4. Janda AM et al., 2015
5. Kutch et al. 2017
6. Hegarty et al. 2020

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COPCs in MAPP: Body map distribution of pain

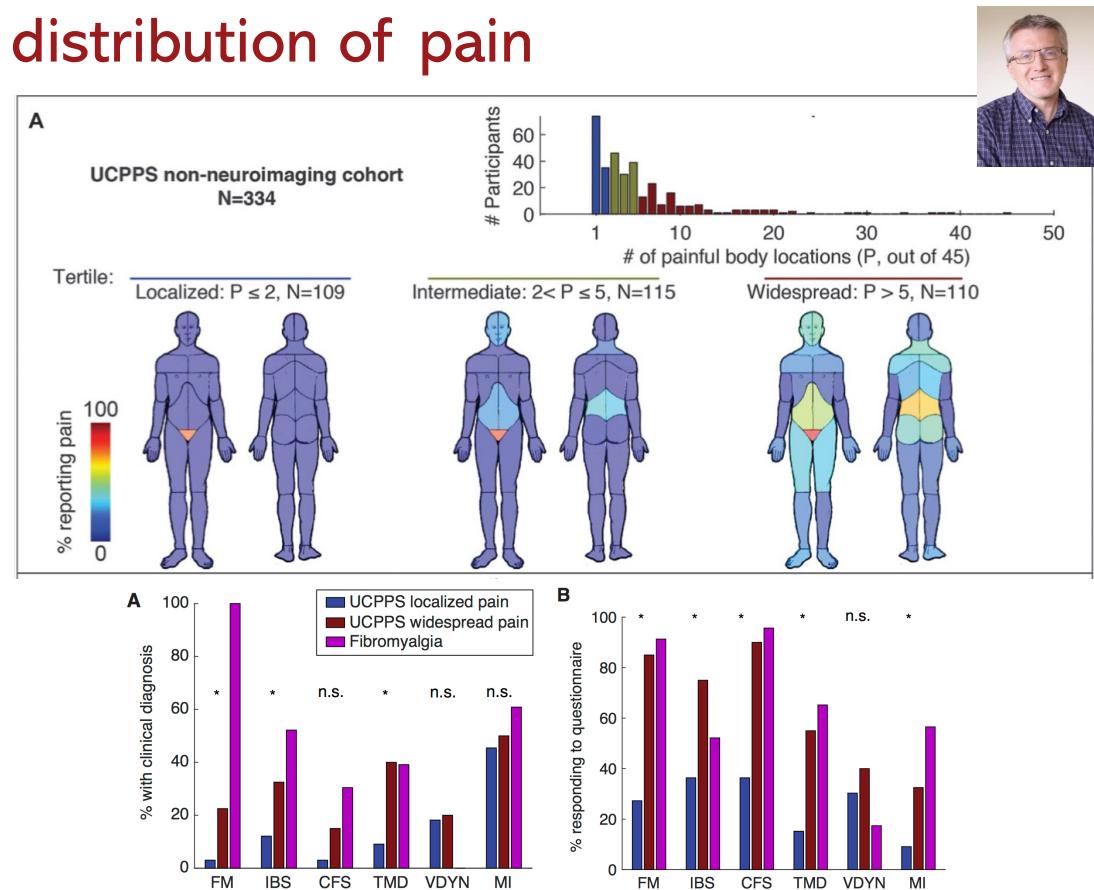
Research Paper

PAIN[®]

Brain signature and functional impact of centralized pain: a multidisciplinary approach to the study of chronic pelvic pain (MAPP) network study

Jason J. Kutch^a, Eric Ichesco^b, Johnson P. Hampson^b, Jennifer S. Labus^c, Melissa A. Farmer^d, Katherine T. Martucci^e, Timothy J. Ness^f, Georg Deutsch^g, A. Vanja Apkarian^d, Sean C. Mackey^b, David J. Klump^h, Anthony J. Schaefferⁱ, Larissa V. Rodriguez^j, Karl J. Kreder^k, Dedra Buchwald^l, Gerald L. Andriole^k, H. Henry Lai^k, Chris Mullins^k, John W. Kusek^k, J. Richard Landis^m, Emeran A. Mayer^c, J. Quentin Clemensⁿ, Daniel J. Clauw^b, Richard E. Harris^{b,*}, for the MAPP Research Network

- Chronic overlapping pain conditions (COPCs) are common in UCPPS
- As pain becomes more widespread in UCPPS patients, it does not do so uniformly, but follows the distribution of the COPCs
- UCPPS patients with widespread pain are more likely to report COPC diagnoses
- UCPPS patients with widespread pain are much more likely to meet questionnaire-based criteria for COPCs



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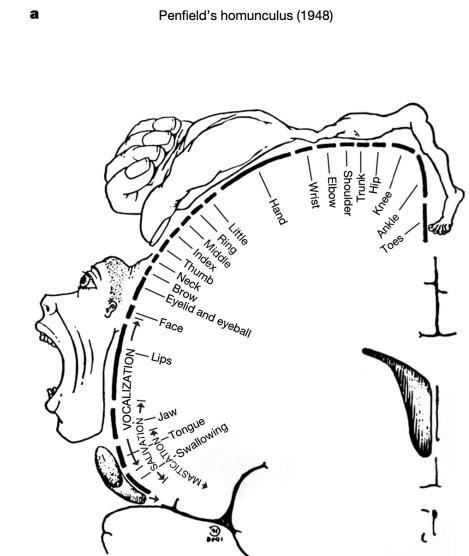
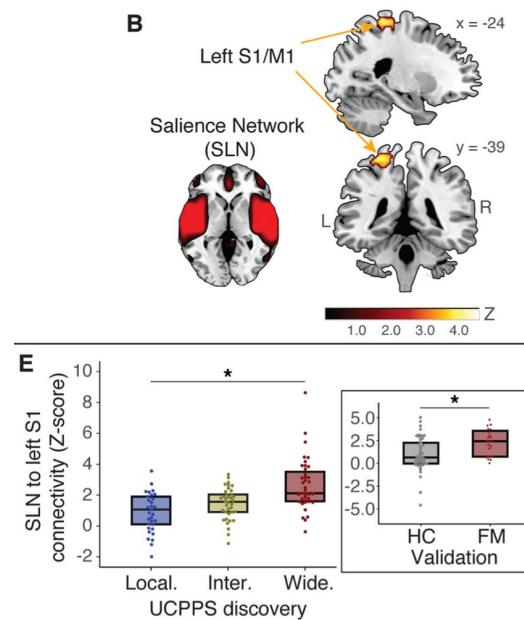
1. Kutch et al. 2017, *Brain Signature ...*

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COPCs in MAPP: neural mechanism (salience/sensorimotor)



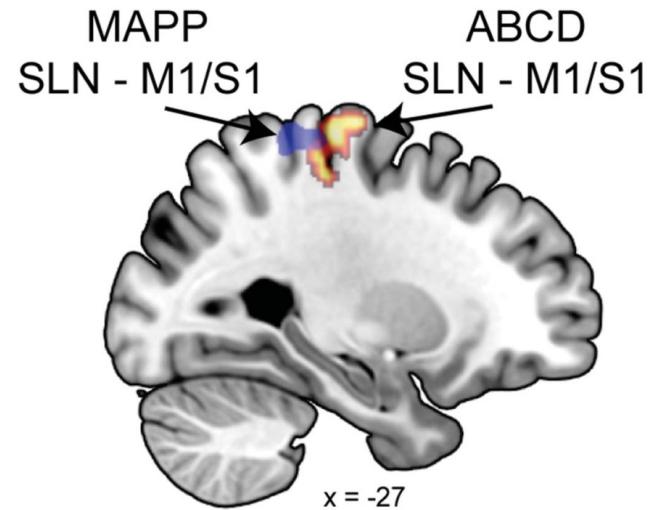
- Analysis of N=110 patients with UCPPS
- Most consistent feature of UCPPS patients with widespread pain was a change in the functional coupling (connectivity) between salience network and a specific sensorimotor (S1/M1) region
- Results were validated in a separate sample of patients with fibromyalgia but not UCPPS
- Puzzling why changes were not distributed across the homunculus, will return to this later in the talk



COPCs in adolescents: salience/sensorimotor connectivity



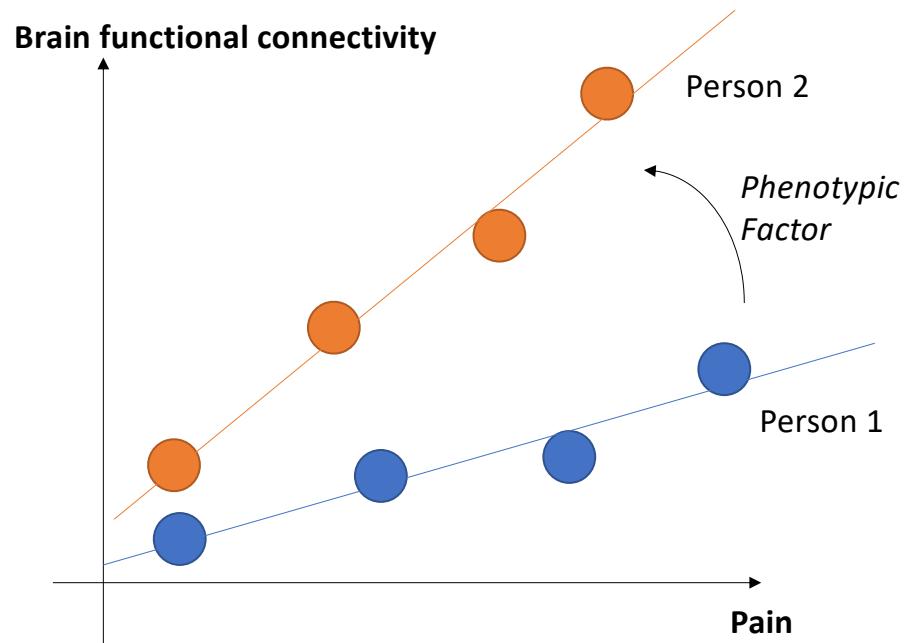
- Chelsea Kaplan and colleagues studied similar phenomenon in adolescents in the Adolescent Brain Cognitive Development (ABCD) study
- Adolescents that developed widespread body pain showed similar changes in S1/M1-salience functional connectivity to MAPP
- These connectivity changes were found before the report of new widespread pain



Approaches to inferring pain centralization



- Quantitative Sensory Testing (QST): May be useful especially if coupled with neuroimaging,¹ but can be difficult to match to the patient's chief complaint
- Animal Models: Critical mechanistic insight,²⁻⁵ but challenges in making direct inference about chronic pain in humans
- Observations of fluctuations in pain intensity coupled with neuroimaging gives an alternative way to examine amplification



MAPP-II: N=492 patients with UCPPS

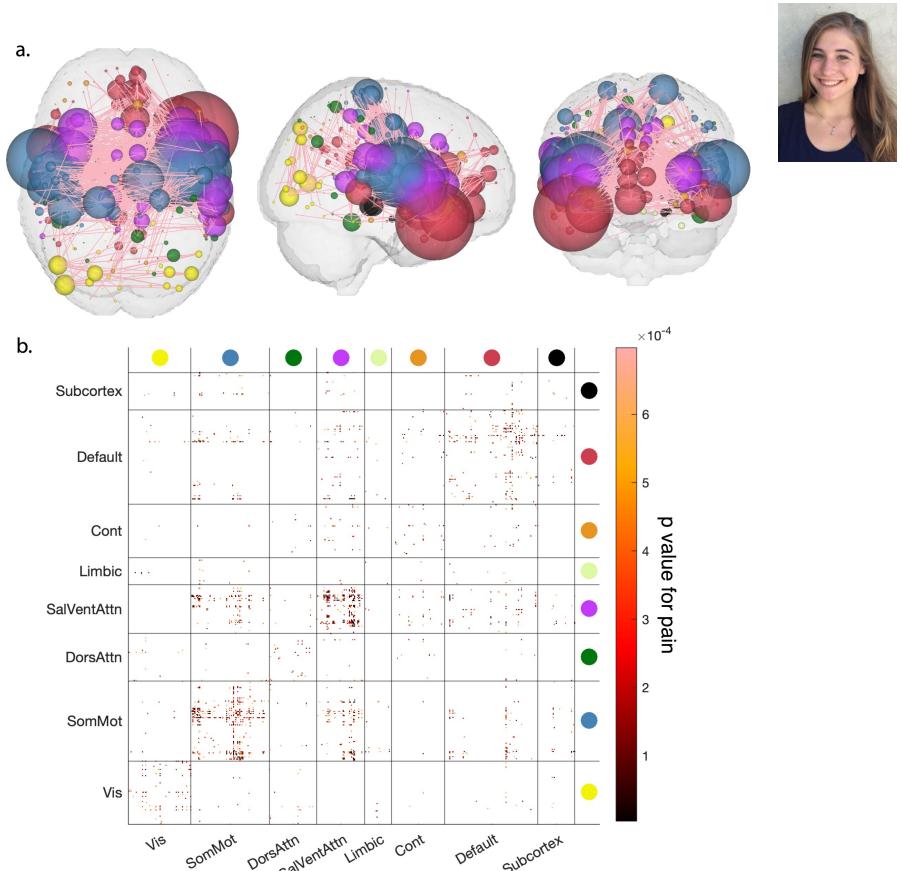


- Major aim of the study was to capture the neural correlates of pain fluctuations in UCPPS
- Here we analyze resting-state correlates of the overall level of genitourinary pain reported by the participant on the day of the scan
- Self-reported pain was highly variable
- Differences in pain were associated with worse physical/mental function and were associated with reports of “flare-ups”

MAPP-II (N=492)		Male (N=177)		Female (N=315)		2020 US Census
Symptom Duration	Age (years)	47.7	(SD) 15.2	42.1	(SD) 15.3	
	Symptom Duration (years)	10.0	10.1	12.7	12.2	
Race		(N)	(%)	(N)	(%)	(%)
	American Indian	2	1.1%	1	0.3%	1.3%
	Asian	1	0.6%	3	1.0%	6.1%
	Black	10	5.6%	19	6.0%	13.6%
	Native Hawaiian	0	0.0%	1	0.3%	0.3%
	White	157	88.7%	276	87.6%	75.8%
	Multi Race	4	2.3%	12	3.8%	2.9%
	Other	3	1.7%	3	1.0%	
	Unknown	0	0.0%	0	0.0%	
Ethnicity						
	Hispanic	12	6.8%	20	6.3%	18.9%
	Non-Hispanic	165	93.2%	294	93.3%	59.3%

Neural correlates of pain

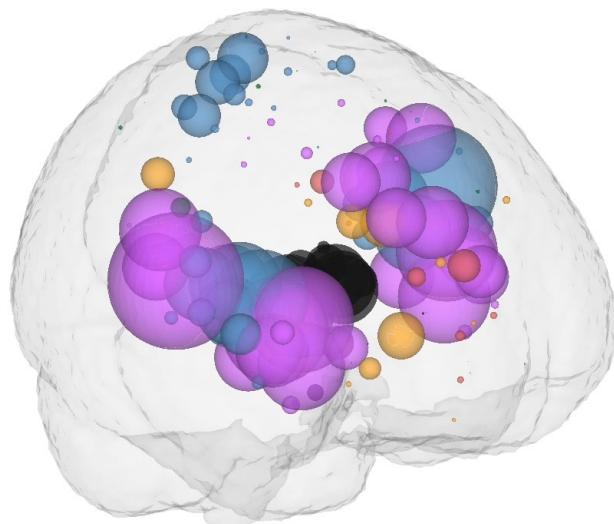
- Examined resting-state functional connectivity using two different atlases
- Functional connectivity values were modeled with a longitudinal mixed effect model focusing on the fixed effect of pain, controlled for age, sex, site, imaging quality, and scan type. FDR corrected for multiple comparisons.
- Connections in the sensorimotor, salience, and default mode networks were significantly correlated with pain intensity, as were connections between sensorimotor and salience network
- Sensorimotor regions were focused primarily in the medial parts of sensorimotor cortex, consistent with the pelvic/bladder representation



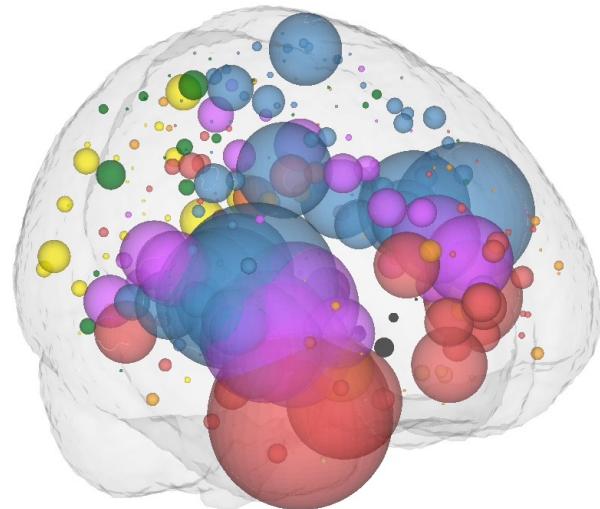
Comparison of Neurosynth to MAPP Longitudinal Analysis



Neurosynth: Pain Studies



MAPP Longitudinal Analysis



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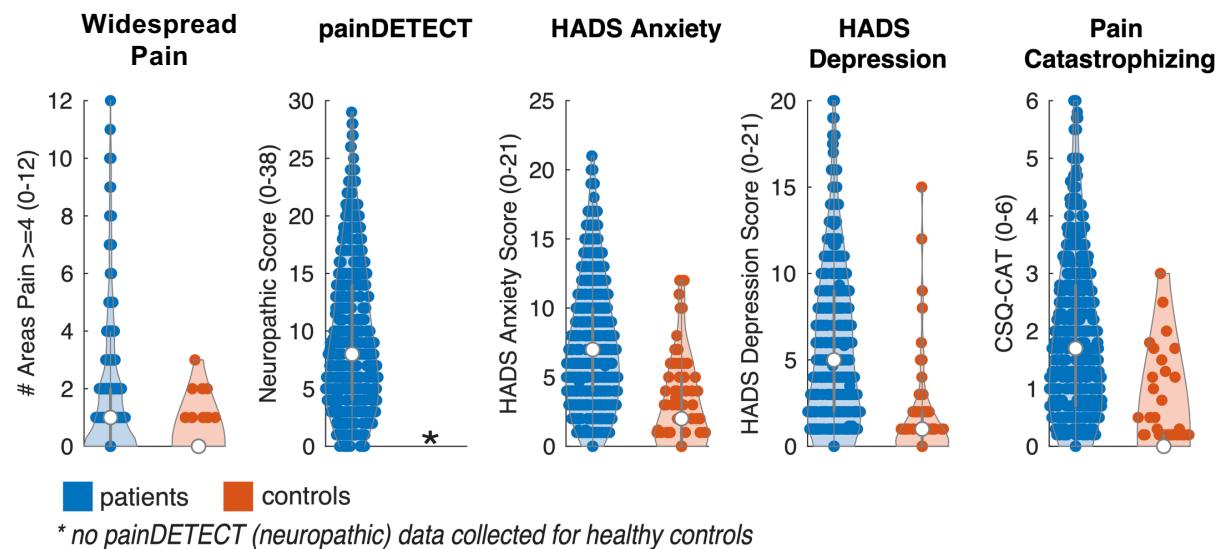
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Potential phenotypic factors of centralized pain



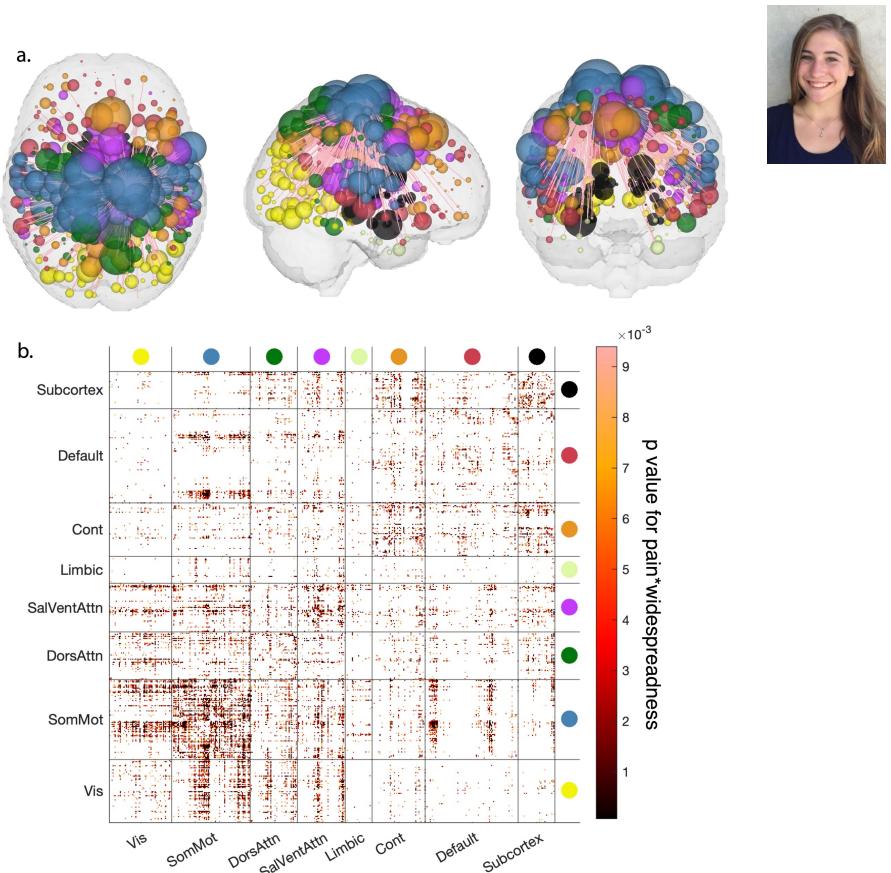
- We examined 5 factors as potential modifiers of the relation between pain and brain connectivity:

- Widespread pain
- Neuropathic pain (painDETECT)
- Anxiety
- Depression
- Catastrophizing

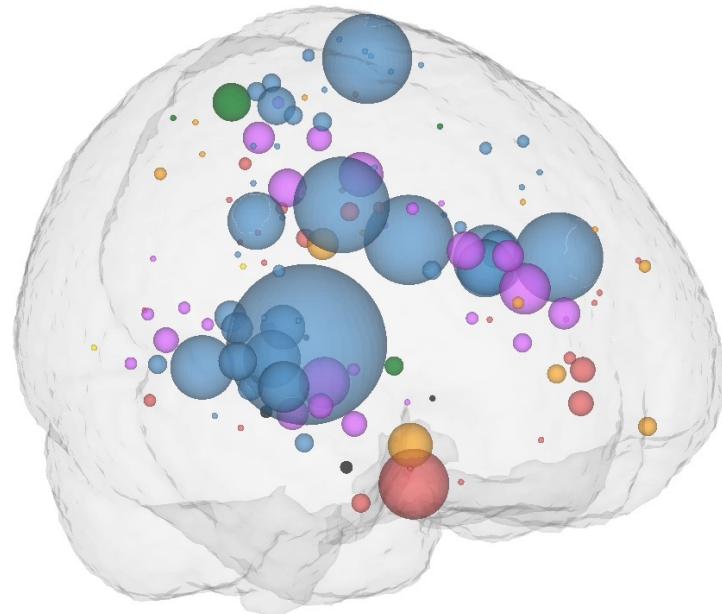


Pain/connectivity correlation modified by widespread pain

- Functional connectivity values were modeled with a longitudinal mixed effect model focusing on the interaction of pain and modifying factor, controlled for age, sex, site, imaging quality, and scan type. FDR corrected for multiple comparisons.
- Presence of widespread pain modified the association between genitourinary pain and functional connectivity across many brain regions/networks
- Modifications were most apparent in the sensorimotor network
- Modifications focused in medial areas of sensorimotor cortex, but it spread out to encompass the entire sensorimotor strip



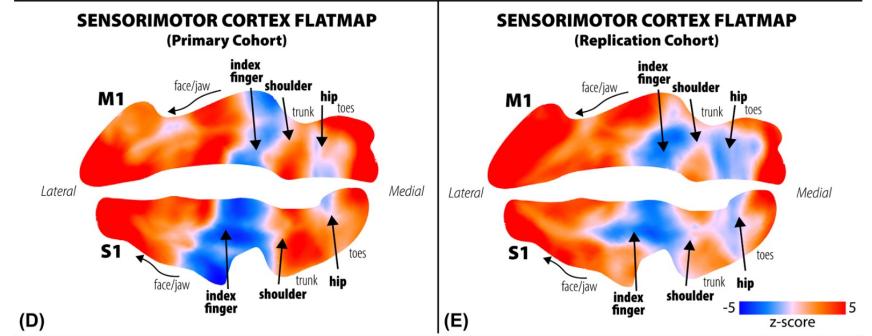
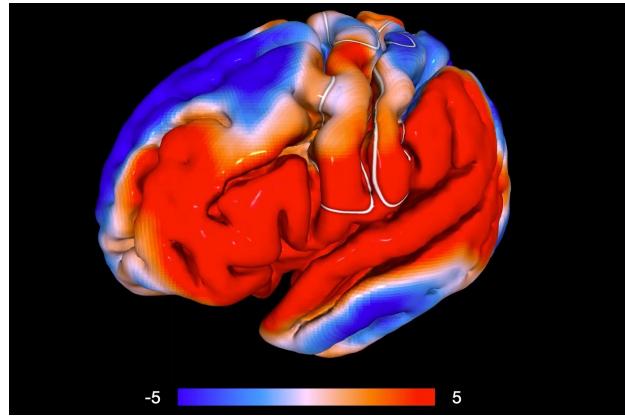
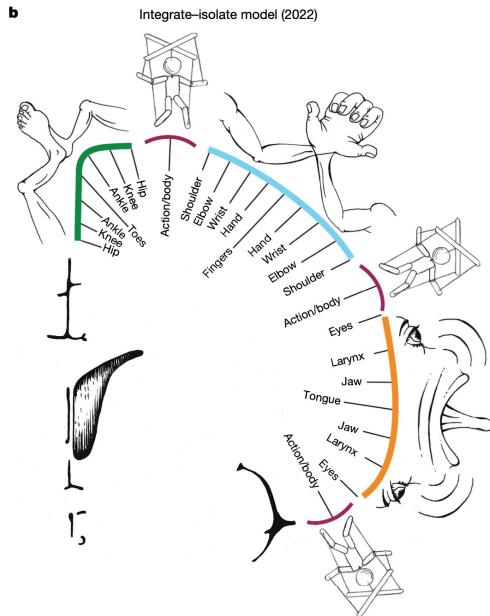
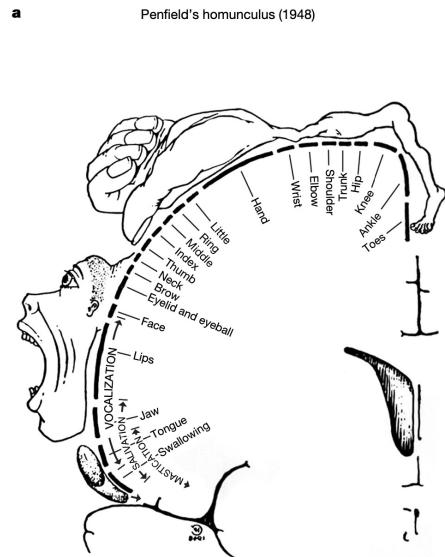
Overlap between pain correlates and widespread modifications



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Spatial inhomogeneities in sensorimotor cortex



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1. Gordon et al. 2023

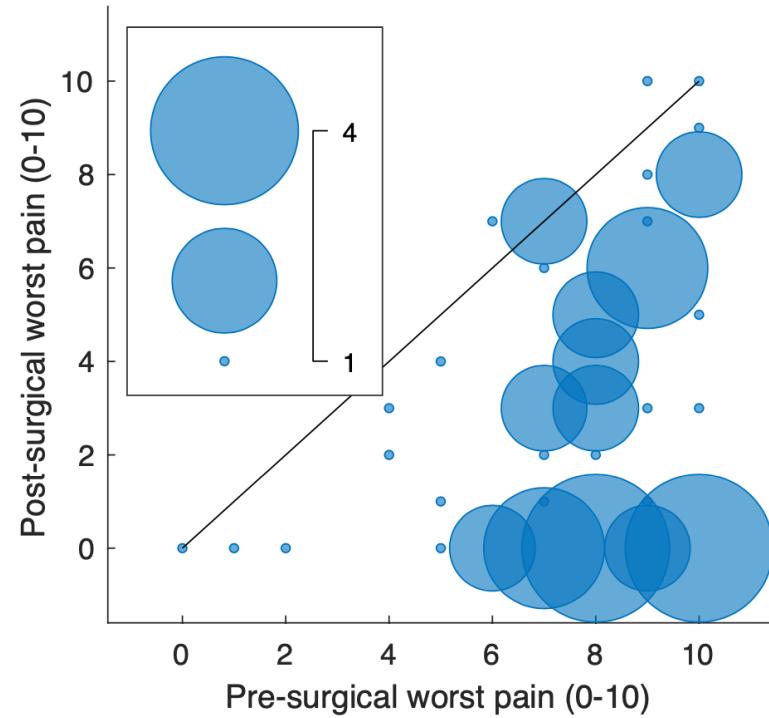
2. Hegarty et al. 2020

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Preliminary surgical response prediction

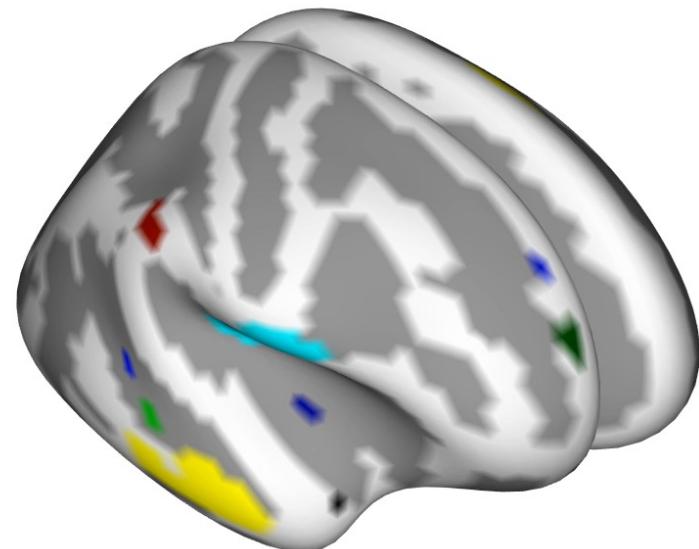
- Collaboration with Andrew Schrepf, Suzie As-Sanie and colleagues at University of Michigan
- N=70 women undergoing surgical hysterectomy for endometriosis
- Average age of 40 years (range 23-50)
- Many patients had their pelvic pain improve substantially, but many had a less successful outcome
- We wanted to ask the question: could pre-surgical brain structure predict surgical response?





Preliminary surgical response prediction

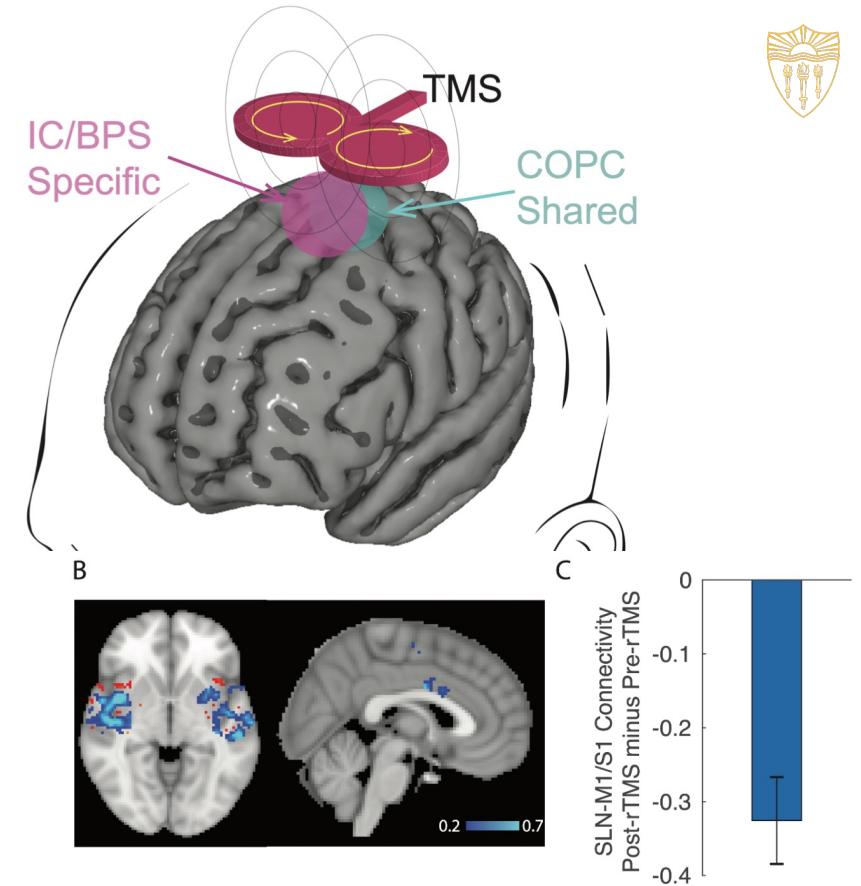
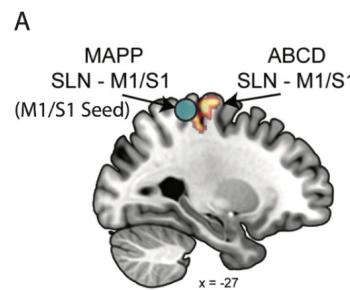
- I previously published with Dr. Schrepf using Freesurfer-derived cortical surface area as an important sub-type classifier in chronic pelvic pain¹. Used the same metric here
- At each vertex, we modelled post-surgical pain as a function of cortical surface area controlled for pre-surgical pain
- We used false discovery rate ($q<0.05$) to correct for multiple comparisons across vertices
- Analysis revealed the possibility of unique prediction of post-surgical pain coming from many pain-related areas: SMA, M1, insula, cingulate



Direct neuromodulation



- In preliminary sample of UCPPS patients (N=7), we examined how HF-rTMS influences the S1/M1-salience functional connectivity
- Seed in M1/S1
- Examine connectivity across salience network mask
- Decreased connectivity observed after rTMS compared to before
- Will be looking at this in larger sample of well-characterized UCPPS patients with COPCs (RO1DK121724)



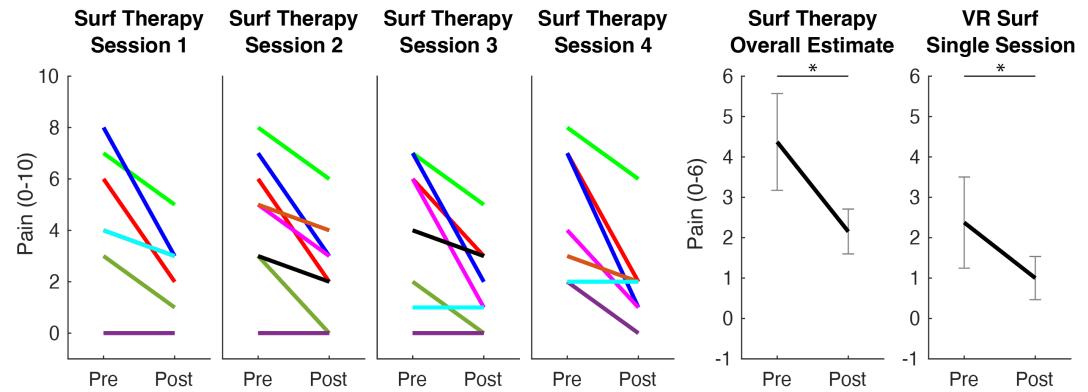
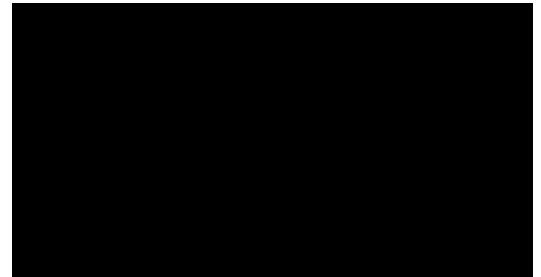
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Neuromodulation of pain through immersive activity



- N=9 UCPPS + COPC
- 6 F, 3M
- Average age 41, range 31-62
- Average symptom duration of 10.3 years, range 3-22
- 4 reported pain with sex, similar to MAPP (41%)



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Conclusions



- Widespread pain currently best clinical marker of central nervous system dysfunction – backed up by objective changes in brain function that are even seen in adolescents that develop widespread pain
- Prediction of heterogeneity in treatment response may give more insights into central nervous system dysfunction.
- Direct neuromodulation with TMS as well as immersive physical activity (including VR) may give means to enhance responsiveness to peripheral therapies

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