Hypermobility, Pain & Neurodivergence

Dr Jessica Eccles @BendyBrain

Clinical Senior Lecturer in Neuroscience, BSMS

Consultant Psychiatrist, Sussex Neurodevelopmental Service

Clinic co-lead SPFT Neurodivergent Brain-Body Clinic

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The big idea
Health, mind and body books

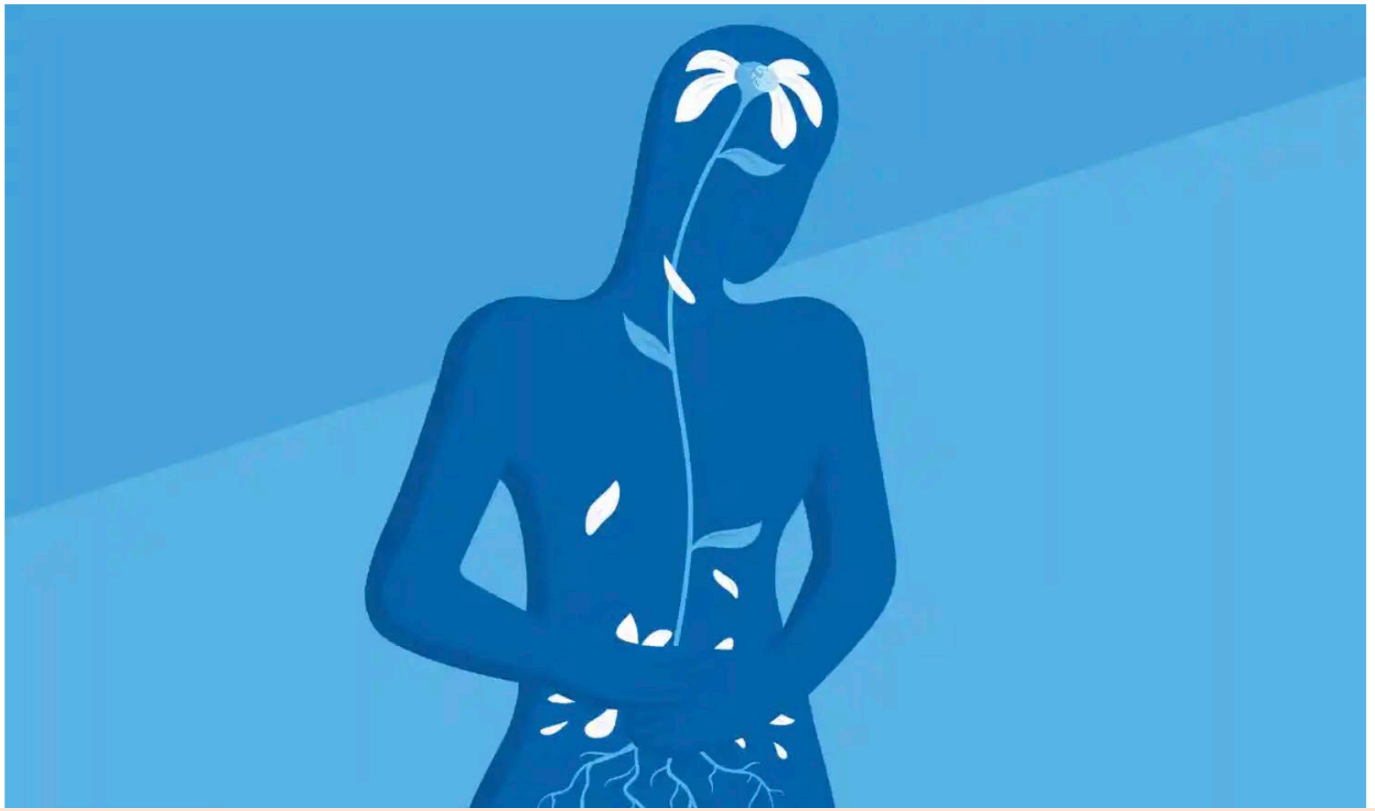
The big idea: should we drop the distinction between mental and physical health?

The current false dichotomy holds back research and stigmatises patients

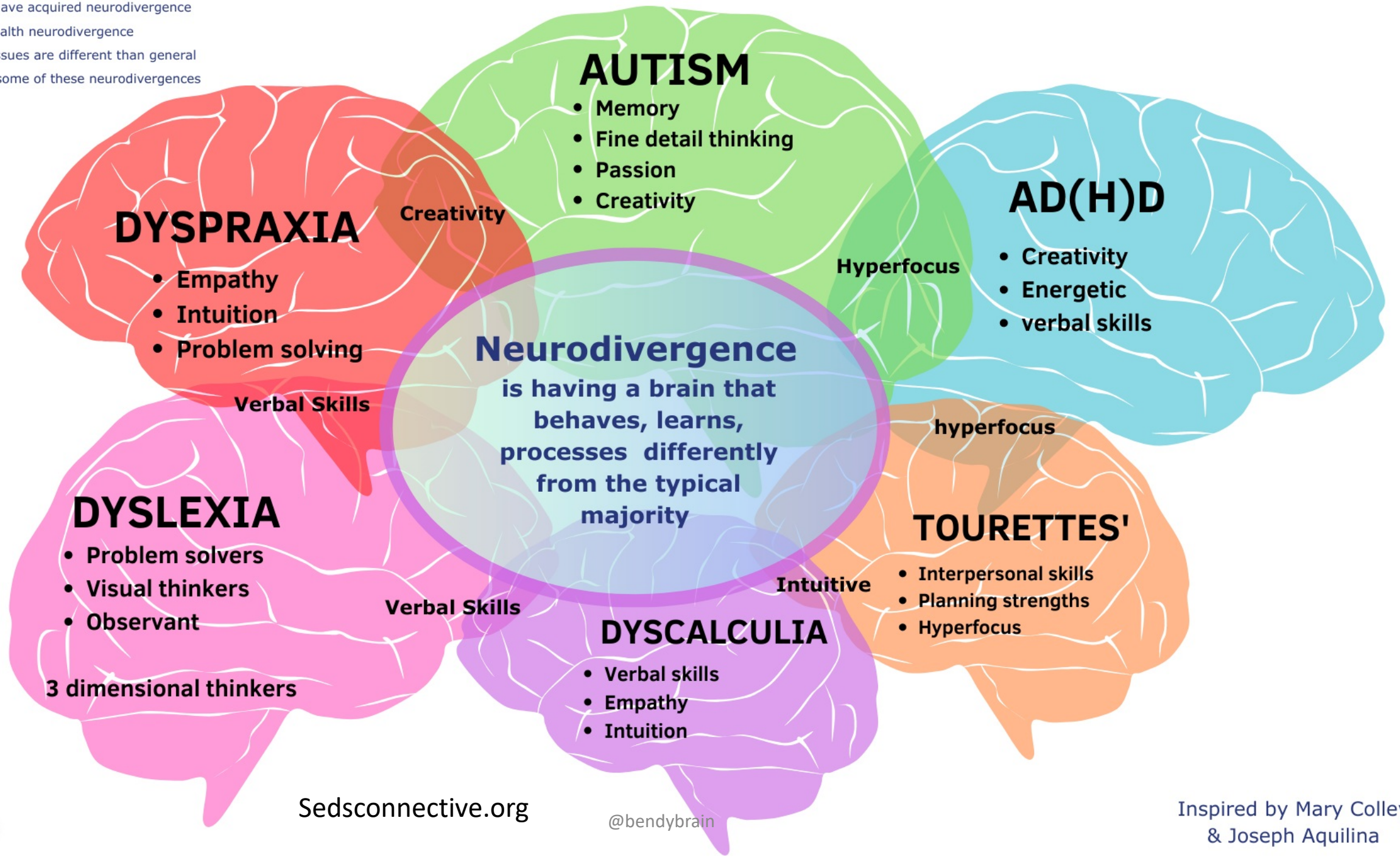
Edward Bullmore

Mon 12 Sep 2022 12.30 BST

147



- You can also have acquired neurodivergence and mental health neurodivergence
- Connective Tissues are different than general population in some of these neurodivergences



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Inspired by Mary Colley & Joseph Aquilina

Learning from clinical practice and research

- Gender stereotypes are complex and a challenge
- Not just boys and bus timetables…..
- Empathy and theory of mind present, perhaps different
- Communication different not inherently ‘disordered’
- Co-occurrence norm rather than exception – both other ND and certain physical health issues
- The language we use is important

RESEARCH ARTICLE

Recognition of Girls on the Autism Spectrum by Primary School Educators: An Experimental Study

Alana Whitlock, Kate Fulton, Meng-Chuan Lai, Elizabeth Pellicano, and William Mandy

Autism has long been considered a predominantly male condition. It is increasingly understood, however, that autistic females are under-recognized. This may reflect gender stereotyping, whereby symptoms are missed in females, because it is assumed that autism is mainly a male condition. Also, some autistic girls and women may go unrecognized because there is a "female autism phenotype" (i.e., a female-typical autism presentation), which does not fit current, male-centric views of autism. Potential biases shown by educators, in their role as gatekeepers for an autism assessment, may represent a barrier to the recognition of autism in females. We used vignettes describing autistic children to test: (a) whether gender stereotyping occurs, whereby educators rate males as more likely to be autistic, compared to females with identical symptoms; (b) whether recognition is affected by sex/gender influences on autistic presentation, whereby children showing the male autism phenotype are rated as more likely to be autistic than those with the female phenotype. Ratings by primary school educators showed a significant main effect of both gender and presentation (male phenotype vs. female phenotype) on estimations of the child in the vignette being autistic: respondents showed a bias against girls and the female autism phenotype. There was also an interaction: female gender had an effect on ratings of the female phenotype, but not on the male phenotype vignette. These findings suggest that primary school educators are less sensitive to autism in girls, through under-recognition of the female autism phenotype and a higher sensitivity to autism in males. ***Autism Res*** *2020, 00: 1–15.* © 2020 The Authors. *Autism Research published by International Society for Autism Research* published by Wiley Periodicals, Inc.

Lay Summary: Educators have an important role in identifying children who need an autism assessment, so gaps in their knowledge about how autism presents in girls could contribute to the under-diagnosis of autistic girls. By asking educators to identify autism when presented with fictional descriptions of children, this study found that educators were less able to recognize what autism "looks like" in girls. Also, when given identical descriptions of autistic boys and girls, educators were more likely to identify autism in boys. These results suggest that primary school educators might need extra help to improve the recognition of girls on the autism spectrum.

Keywords: autism; sex; gender; female; stereotype; recognition; teacher; educator

ELSEVIER

Biological Psychiatry

Volume 92, Issue 8, 15 October 2022, Pages e35-e36

Early Career Investigator Commentary

Balanced Sex Ratios and the Autism Continuum

Aneta Krakowski

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https://doi.org/10.1016/j.biopsych.2022.07.020

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Refers to

A Data-Driven Approach in an Unbiased Sample Reveals Equivalent Sex Ratio of Autism Spectrum Disorder–Associated Impairment in Early...

Biological Psychiatry, Volume 92, Issue 8, 15 October 2022, Pages 654-662

Catherine A. Burrows, Rebecca L. Grzadzinski, Kevin Donovan, Isabella C. Stallworthy, Joshua Rutsohn, Tanya St. John, Natasha Marrus, Julia Parish-Morris, Leigh MacIntyre, Jacqueline Hampton, Juhi Pandey, Mark D. Shen, Kelly N. Botteron, Annette M. Estes, Stephen R. Dager, Heather C. Hazlett, John R. Pruett, Robert T. Schultz, Lonnie Zwaigenbaum, Kinh N. Truong, Joseph Piven, Jed T. Elison

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Autism is a heterogeneous neurodevelopmental condition that is diagnosed more frequently in males than females (note that in this commentary, the use of "female" and "male" refers to sex assigned at birth). The ratio of male to female diagnosis is about 3.25 to 1 when evaluated using ascertainment methods that actively screen a population-based sample, compared with the 4.56 to 1 ratio in individuals who have already had a diagnosis of autism (1). In many cases, females tend to not receive a diagnosis of autism until later in life when they have increased difficulties navigating a more complex social environment, or they tend to receive co-occurring diagnoses early in life that overshadow their autism.

Females may receive a delayed diagnosis or be underdiagnosed, as autistic presentations

General practice / Family practice
Original research

Barriers to healthcare and self-reported adverse outcomes for autistic adults: a cross-sectional study

Mary Doherty [1], Stuart Neilson [2], Jane O'Sullivan [3], Laura Carravallah [4], Mona Johnson [5], Walter Cullen [6], Sebastian C K Shaw [7]

Correspondence to Dr Mary Doherty; drmdoherty@gmail.com

Abstract

Objectives Autistic people experience poor physical and mental health along with reduced life expectancy compared with non-autistic people. Our aim was to identify self-reported barriers to primary care access by autistic adults compared with non-autistic adults and to link these barriers to self-reported adverse health consequences.

Design Following consultation with the autistic community at an autistic conference, *Autscape*, we developed a self-report survey, which we administered online through social media platforms.

Setting A 52-item, international, online survey.

Participants 507 autistic adults and 157 non-autistic adults.

Primary and secondary outcome measures Self-reported barriers to accessing healthcare and associated adverse health outcomes.

Results Eighty per cent of autistic adults and 37% of non-autistic respondents reported difficulty visiting a general practitioner (GP). The highest-rated barriers by autistic adults were deciding if symptoms warrant a GP visit (72%), difficulty making appointments by telephone (62%), not feeling understood (56%), difficulty communicating with their doctor (53%) and the waiting room environment (51%). Autistic adults reported a preference for online or text-based appointment booking, facility to email in advance the reason for consultation, the first or last clinic appointment and a quiet place to wait. Self-reported adverse health outcomes experienced by autistic adults were associated with barriers to accessing healthcare. Adverse outcomes included untreated physical and mental health conditions, not attending specialist referral or screening programmes, requiring more extensive treatment or surgery due to late presentations and untreated potentially life-threatening conditions. There were no significant differences in difficulty attending, barriers experienced or adverse outcomes between formally diagnosed and self-identified autistic respondents.

Conclusions Reduction of healthcare inequalities for autistic people requires that healthcare providers understand autistic perspectives, communication needs and sensory sensitivities. Adjustments for autism-specific needs are as necessary as ramps for wheelchair users.

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What type of service do you work in?

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What sort of physical health issues do your patients have?

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Autism is not just for specialists

“In this study, all new patients referred to an adult psychiatric outpatient clinic in Sweden between November 2019 and October 2020 (n = 562) were screened for autism using the Ritvo Autism and Asperger Diagnostic Scale Screen (RAADS-14).

They estimated the prevalence of autism in this population to at least 18.9%” [1]

[1]: Nuyrenis et al., 2022

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Do you think it would be a good idea for Autism services to also assess for ADHD

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What would the challenges be?

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What percentage of autisic patients have co-occurent ADHD

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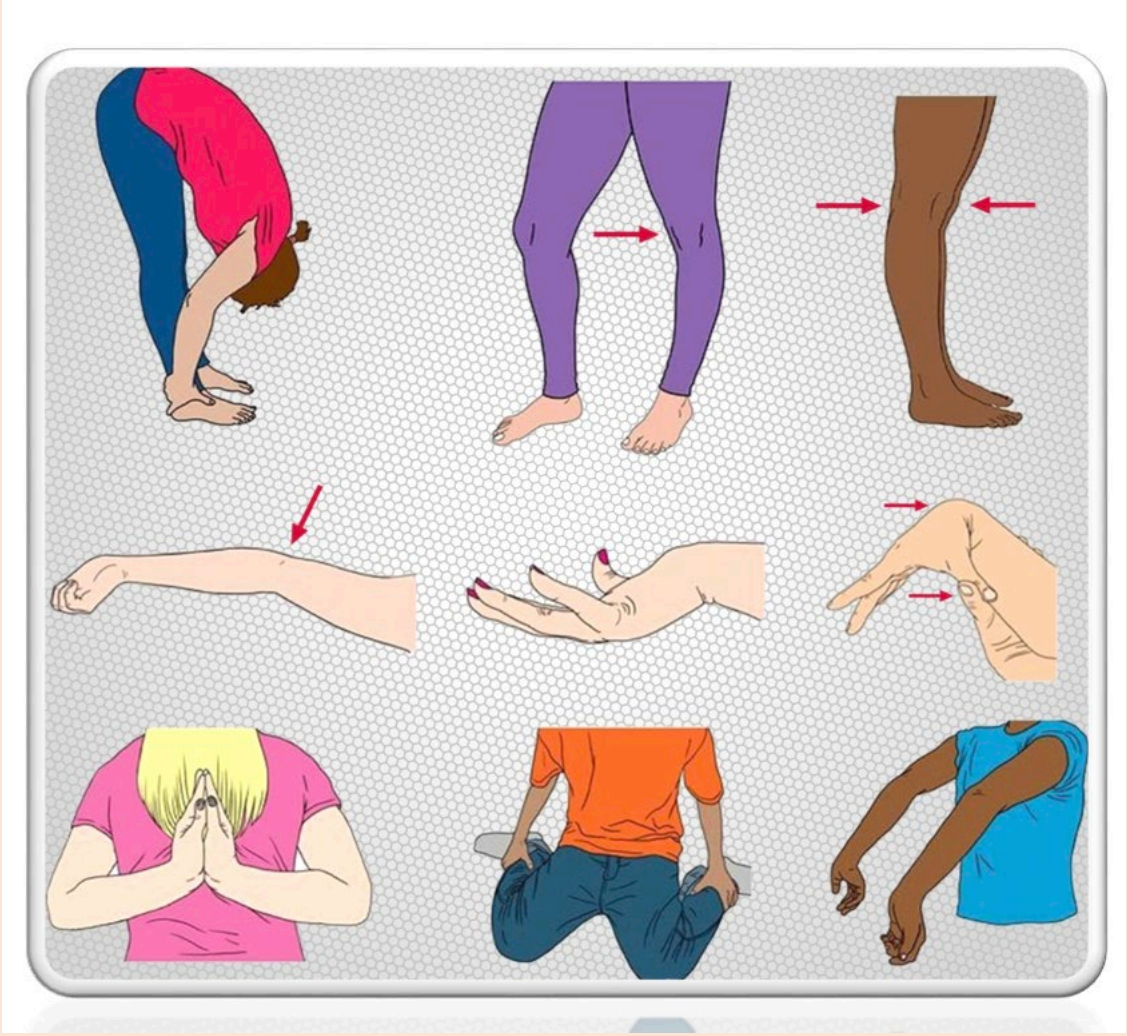
Co-occurrence

- Overlap with other NDCs is common including up to 66% co-occurrence with ADHD
- In chronic tic conditions (e.g., Tourette syndrome) there is 60% overlap with other NDCs
- **4 in 5 autistics also have dyspraxia**
- **1 in 2 people with DCD have ADHD**

A lightbulb moment

?



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How many are familiar with how to screen for this condition?

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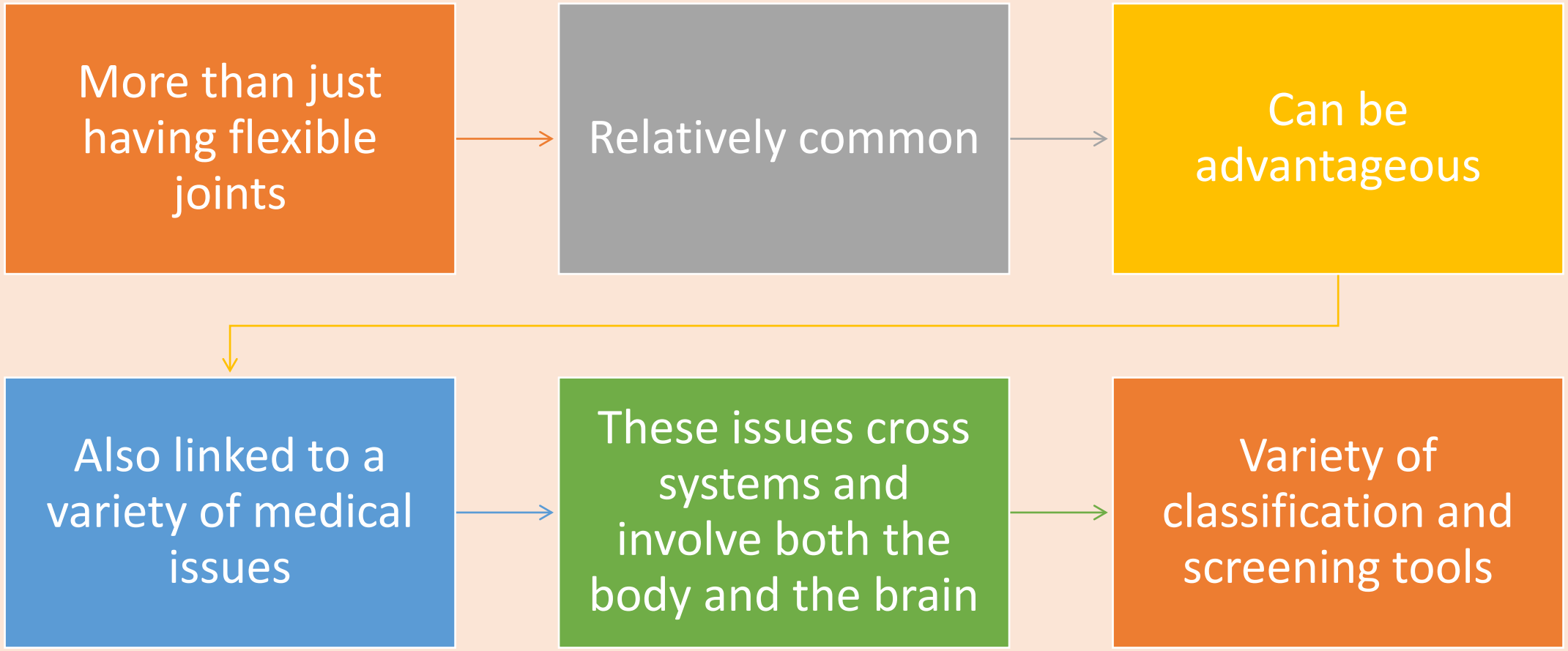
Hypermobility



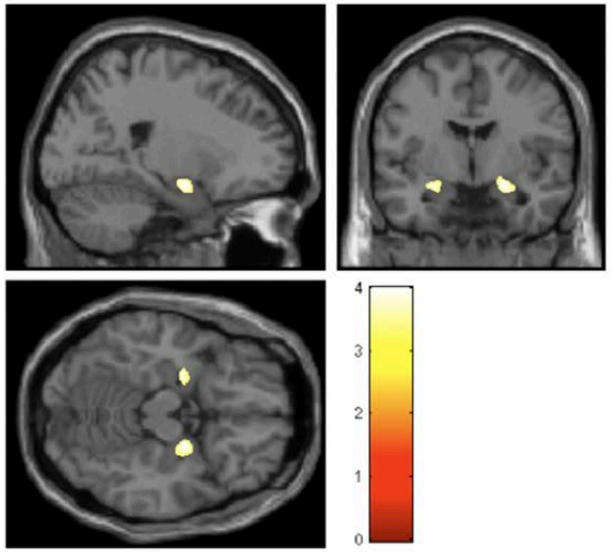
Criterion 1 can be met if 2 or more questions are positive on the self-report scale of Hakim and Grahame (2003):

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself "double jointed"?

Table 3
Clinical Spectrum of EDS-HT/JHS (Hamonet et al., 2014; Colombi et al., 2015).

Osteoarticular	i.e. mild scoliosis, flat foot, lumbar hyperlordosis, joint hypermobility
Muscular	i.e. hypotonia, fibromyalgia, recurrent myalgias and cramps, dystonia
Mucocutaneous	i.e. mildly hyperextensible skin, velvety/silky/soft skin texture, striae rubrae and/or distensae in young age, small or post-surgical atrophic scars, Keratosis pilaris, hernias, light blue sclerae, gingival inflammation/recessions, hypoplastic lingual frenulum, easy bruising, resistance to local anaesthetic drugs
Gastrointestinal	i.e. dysphagia, dysphonia, reflux gastroesophageal, gastritis, unexplained abdominal pain, food intolerances
Cardiovascular	i.e. varicose veins, low progressive aortic root dilatation, pseudo-Raynaud's phenomenon, mitral valve prolapse
Urogynaecological	i.e. dyspareunia, dysmenorrhea, urinary stress incontinence, meno/metrorrhagia.
Ocular	i.e. myopia, strabismus, palpebral ptosis.
Dental	i.e. dental neuralgia, gingivitis, temporo mandibular joint pain, dental pains to cold/warm.
Neuropsychiatric	i.e. dysautonomia, clumsiness, proprioceptive dysfunction, paresthesia, headache, fatigue, sleep disturbances, cognitive impairment, anxiety, hyperaesthesia, hyperosmia, hyperacousis.


Pain
DO YOU WORRY OVER MINOR MATTERS?
Do people call you a
Hypochondr
DO YOU HAVE PANIC ATTACKS?
Do you experience episodes of
• Fear and anxiety
ANXIETY RESEARCH
18-50 years old inclus
If you feel tense, irritable, have tr
concentrating, find yourself worrying
over small matters, have difficulty
upset st
beat....
Anxiety
If you are 60 years or older and depressed, you may qualify
by the National Institute of
DEPRESSED?
A research study for adults who suffer f
PANIC ATTACKS
DEPRESSED?
• Fear and anxiety • Heart Pounding
shortness of breath
DEPRESSION
f you are 18 to 60 years old.
ession, and have tried antid
you may be eligible to par
l research study with an inve
PANIC ATTA
Women, age 21-45 yrs)
needed for 7-8 week inpatient
study of medication
DEPRESSION!
A research study for adults who suffer from
PANIC ATTACKS
shortness of breath, pounding
heart, dizziness, or fear of dying?
Do you suffer from
DEPRESSION?
ANXIETY?
DO YOU WORRY OVER MINOR MATTERS?
all the time?
concentrating?
3 FREE
DEPRESSED?



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BJPsych The British Journal of Psychiatry

Brain structure and joint hypermobility: relevance to the expression of psychiatric symptoms

Jessica A. Eccles, Felix D. C. Beacher, Marcus A. Gray, Catherine L. Jones, Ludovico Minati, Neil A. Harrison and Hugo D. Critchley

BJP 2012, 200:508-509.
Access the most recent version at DOI: 10.1192/bjp.bp.111.092460

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Variant connective tissue (joint hypermobility) and its relevance to depression and anxiety in adolescents: a cohort-based case–control study

Jessica A Eccles [1, 2], Lisa Quadt [1, 2], Hannah McCarthy [1, 3], Kevin A Davies [4], Rod Bond [5], Anthony S David [6], Neil A Harrison [1, 7], Hugo D Critchley [1, 2]

Correspondence to Dr Jessica A Eccles; j.eccles@bsms.ac.uk

Abstract

Objective To test whether variant connective tissue structure, as indicated by the presence of joint hypermobility, poses a developmental risk for mood disorders in adolescence.

Design Cohort-based case–control study.

Setting Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) were interrogated.

Participants 6105 children of the ALSPAC cohort at age 14 years old, of whom 3803 also were assessed when aged 18 years.

Main outcome measures In a risk analysis, we examined the relationship between generalised joint hypermobility (GJH) at age 14 years with psychiatric symptoms at age 18 years. In an association analysis, we examined the relationship between presence of symptomatic joint hypermobility syndrome (JHS) and International Classification of Diseases-10 indication of depression and anxiety (Clinical Interview Schedule Revised (CIS-R), Anxiety Sensitivity Index) at age 18 years.

Results GJH was more common in females (n=856, 28%) compared with males (n=319, 11%; OR: 3.20 (95% CI: 2.78 to 3.68); p<0.001). In males, GJH at age 14 years was associated with depression at 18 years (OR: 2.10 (95% CI: 1.17 to 3.76); p=0.013). An index of basal physiological arousal, elevated resting heart rate, mediated this effect. Across genders, the diagnosis of JHS at age 18 years was associated with the presence of depressive disorder (adjusted OR: 3.53 (95% CI: 1.67 to 7.40); p=0.001), anxiety disorder (adjusted OR: 3.14 (95% CI: 1.52 to 6.46); p=0.002), level of anxiety (B=8.08, $t(3278)=3.95$; p<0.001) and degree of psychiatric symptomatology (B=5.89, $t(3442)=5.50$; p<0.001).

Conclusions Variant collagen, indexed by joint hypermobility, is linked to the emergence of depression and anxiety in adolescence, an effect mediated by autonomic factors in males. Recognition of this association may motivate further evaluation, screening and interventions to mitigate development of psychiatric disorders and improve health outcomes.

Review > World J Psychiatry. 2021 Oct 19;11(10):805-820. doi: 10.5498/wjp.v11.i10.805.

Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression

Harriet Emma Clare Sharp [1], Hugo D Critchley [2], Jessica A Eccles [1]

Affiliations + expand

PMID: 34733643 PMCID: PMC8546774 DOI: 10.5498/wjp.v11.i10.805

Free PMC article

Commonalities
Hypermobility and ND

- Dysautonomia
- Pain
- Dyspraxia
- Anxiety
- Case control studies in childre: ADHD, Dyspraxia

Cederlöf et al. BMC Psychiatry (2016) 16:207
DOI 10.1186/s12888-016-0922-6

BMC Psychiatry

RESEARCH ARTICLE Open Access

Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers–Danlos syndrome or hypermobility syndrome and their siblings

Martin Cederlöf[1*], Henrik Larsson[1], Paul Lichtenstein[1], Catarina Almqvist[1,2], Eva Serlachius[3] and Jonas F. Ludvigsson[1,4,5,6]

Abstract

Background: To assess the risk of psychiatric disorders in Ehlers-Danlos syndrome (EDS) and hypermobility syndrome.

Methods: Nationwide population-based matched cohort study. EDS, hypermobility syndrome and psychiatric disorders were identified through Swedish national registries. Individuals with EDS ($n = 1,771$) were matched with comparison individuals ($n = 17,710$). Further, siblings to individuals with EDS who did not have an EDS diagnosis themselves were compared with matched comparison siblings. Using conditional logistic regression, risk of autism spectrum disorder (ASD), bipolar disorder, attention deficit hyperactivity disorder (ADHD), depression, attempted suicide, suicide and schizophrenia were estimated. The same analyses were conducted in individuals with hypermobility syndrome ($n = 10,019$) and their siblings.

Results: EDS was associated with ASD: risk ratio (RR) 7.4, 95 % confidence interval (95 % CI) 5.2–10.7; bipolar disorder: RR 2.7, CI 1.5–4.7; ADHD: RR 5.6, CI 4.2–7.4; depression: RR 3.4, 95 % CI 2.9–4.1; and attempted suicide: RR 2.1, 95 % CI 1.7–2.7, but not with suicide or schizophrenia. EDS siblings were at increased risk of ADHD: RR 2.1, 95 % CI 1.4–3.3; depression: RR 1.5, 95 % CI 1.1–1.8; and suicide attempt: RR 1.8, 95 % CI 1.4–2.3. Similar results were observed for individuals with hypermobility syndrome and their siblings.

Conclusions: Individuals with EDS and hypermobility syndrome are at increased risks of being diagnosed with psychiatric disorders. These risk increases may have a genetic and/or early environmental background as suggested by evidence showing that siblings to patients have elevated risks of certain psychiatric disorders.

Keywords: Cohort study, Ehlers-Danlos syndrome, Hypermobility syndrome, Epidemiology, Psychiatric disorders

Review Article | Published: 14 February 2018

Attention-deficit/hyperactivity disorder, joint hypermobility-related disorders and pain: expanding body-mind connections to the developmental age

Carolina Baeza-Velasco, Lorenzo Sinibaldi & Marco Castori

ADHD Attention Deficit and Hyperactivity Disorders **10**, 163–175 (2018) | Cite this article

REVIEW article

Front. Psychiatry, 07 December 2018
Sec. Child and Adolescent Psychiatry
https://doi.org/10.3389/fpsyt.2018.00656

This article is part of the Research Topic
Comorbidity and Autism Spectrum Disorder
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Autism, Joint Hypermobility-Related Disorders and Pain



Carolina Baeza-Velasco[1,2*], David Cohen[3,4], Claude Hamonet[5], Elodie Vlamynck[6], Lautaro Diaz[3], Cora Cravero[3], Emilie Cappe[1] and Vincent Guinchat[3]

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Jessica A Eccles [1, 2], Lisa Quadt [1, 2], Hannah McCarthy [1, 3], Kevin A Davies [4], Rod Bond [5], Anthony S David [6], Neil A Harrison [1, 7], Hugo D Critchley [1, 2]

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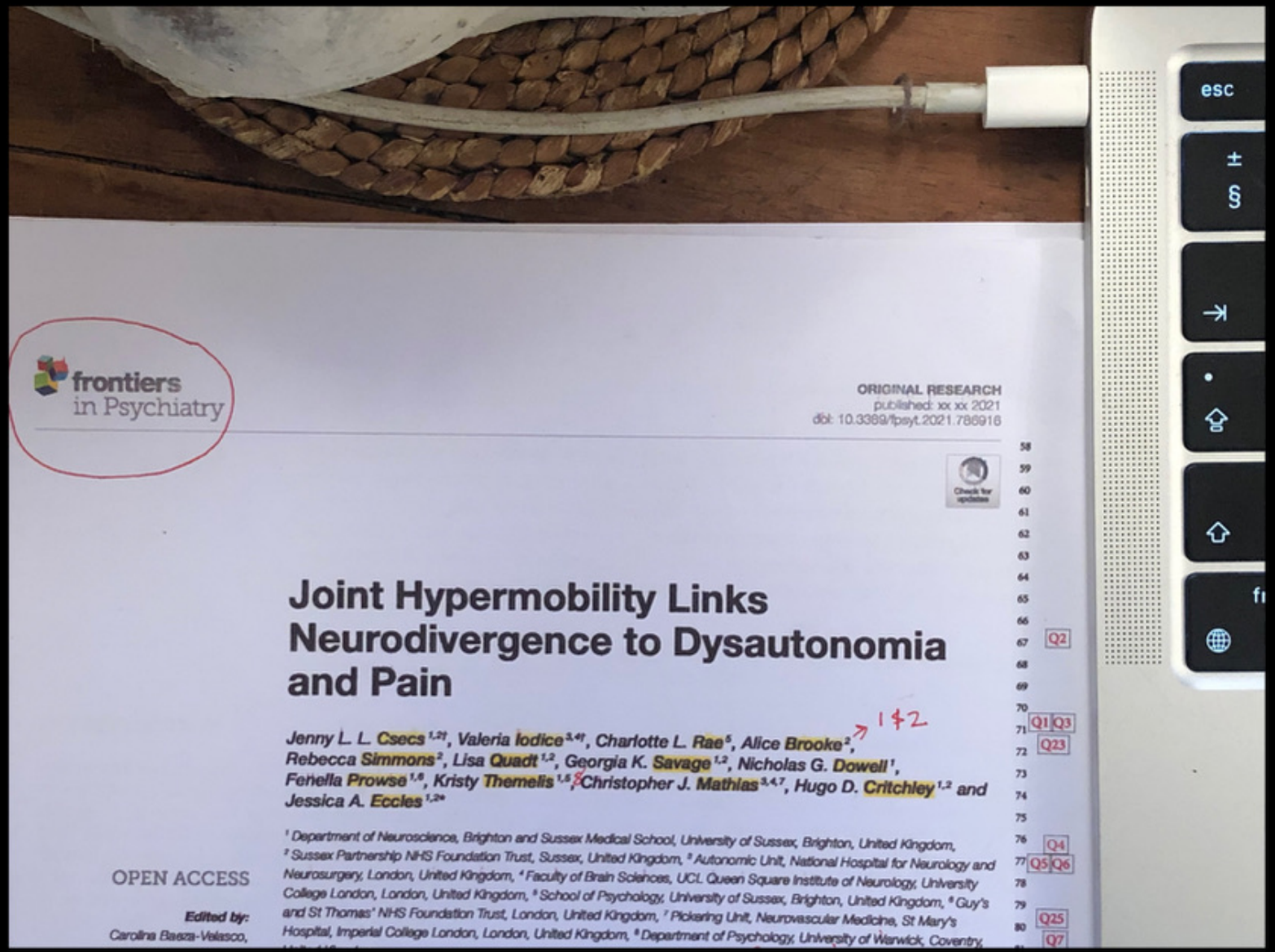

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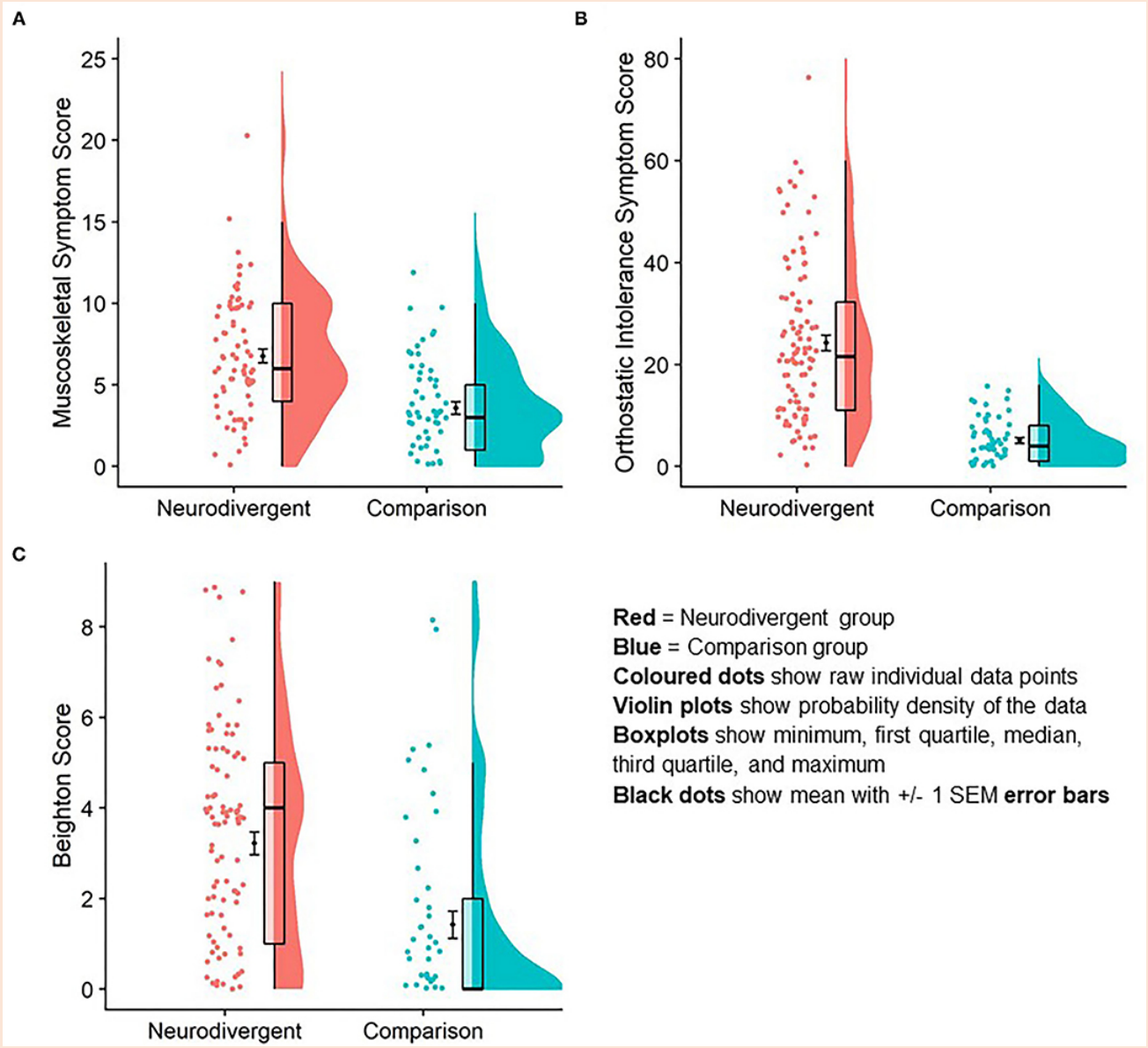
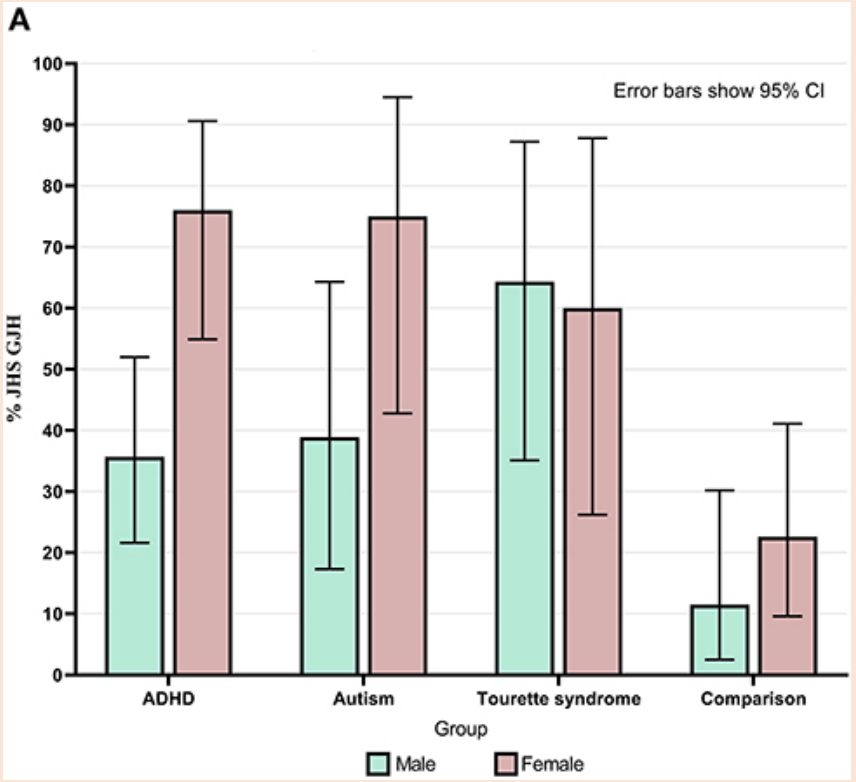
- OR HM in ND 4.51 (95% CI 2.17–9.37) c.f general population
- ND greater orthostatic intolerance and musculoskeletal skeletal pain
- HM mediates this link

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ADHD
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Comparison
Group
Male
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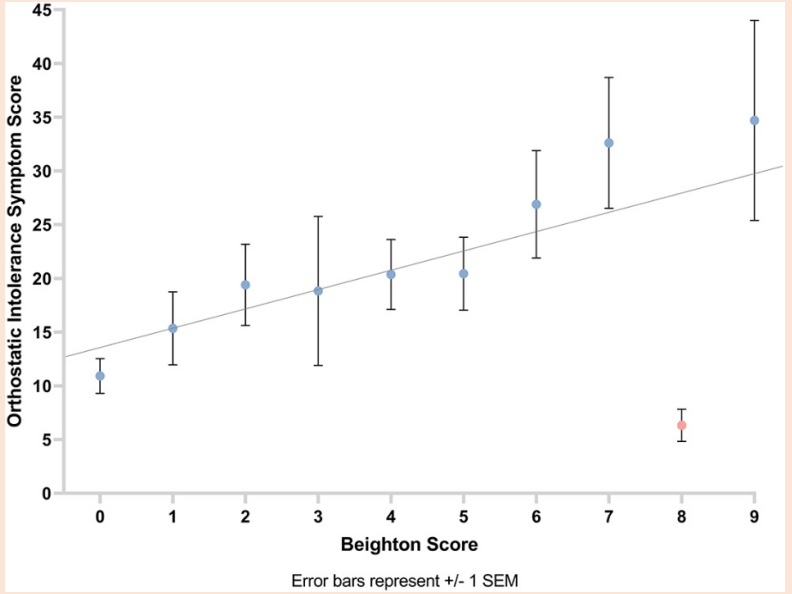
Orthostatic Intolerance Symptom Score
45
40
35
30
25
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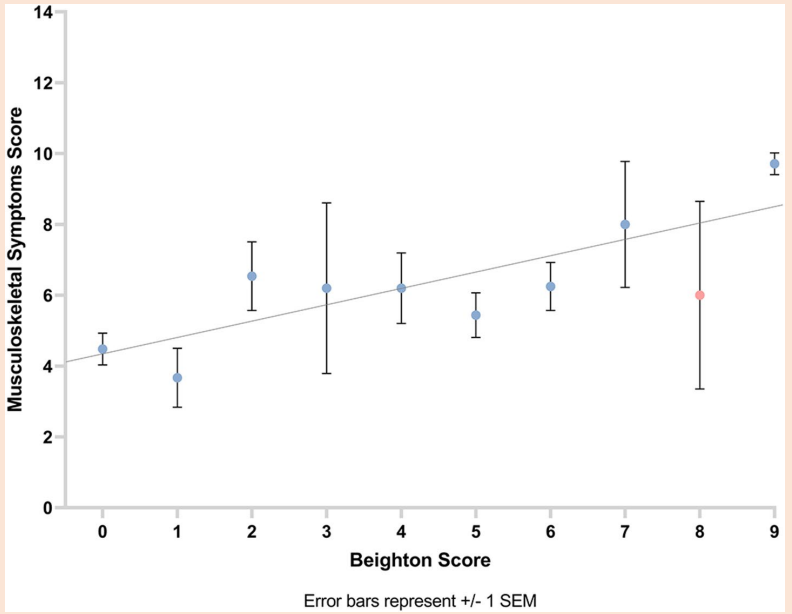
6
7
8
9
Beighton Score
Error bars represent +/- 1 SEM


Musculoskeletal Symptoms Score
14
12
10
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7
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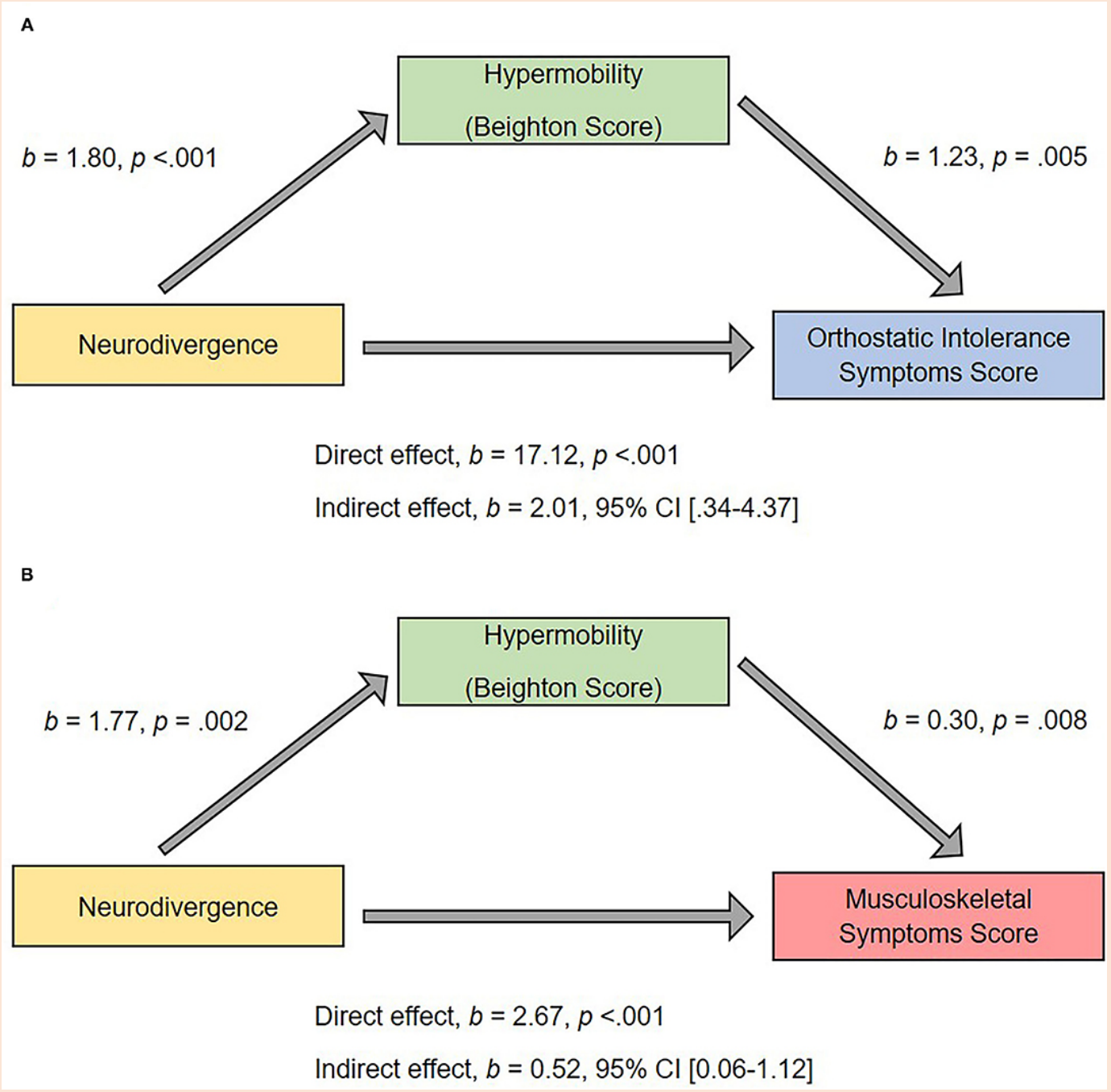
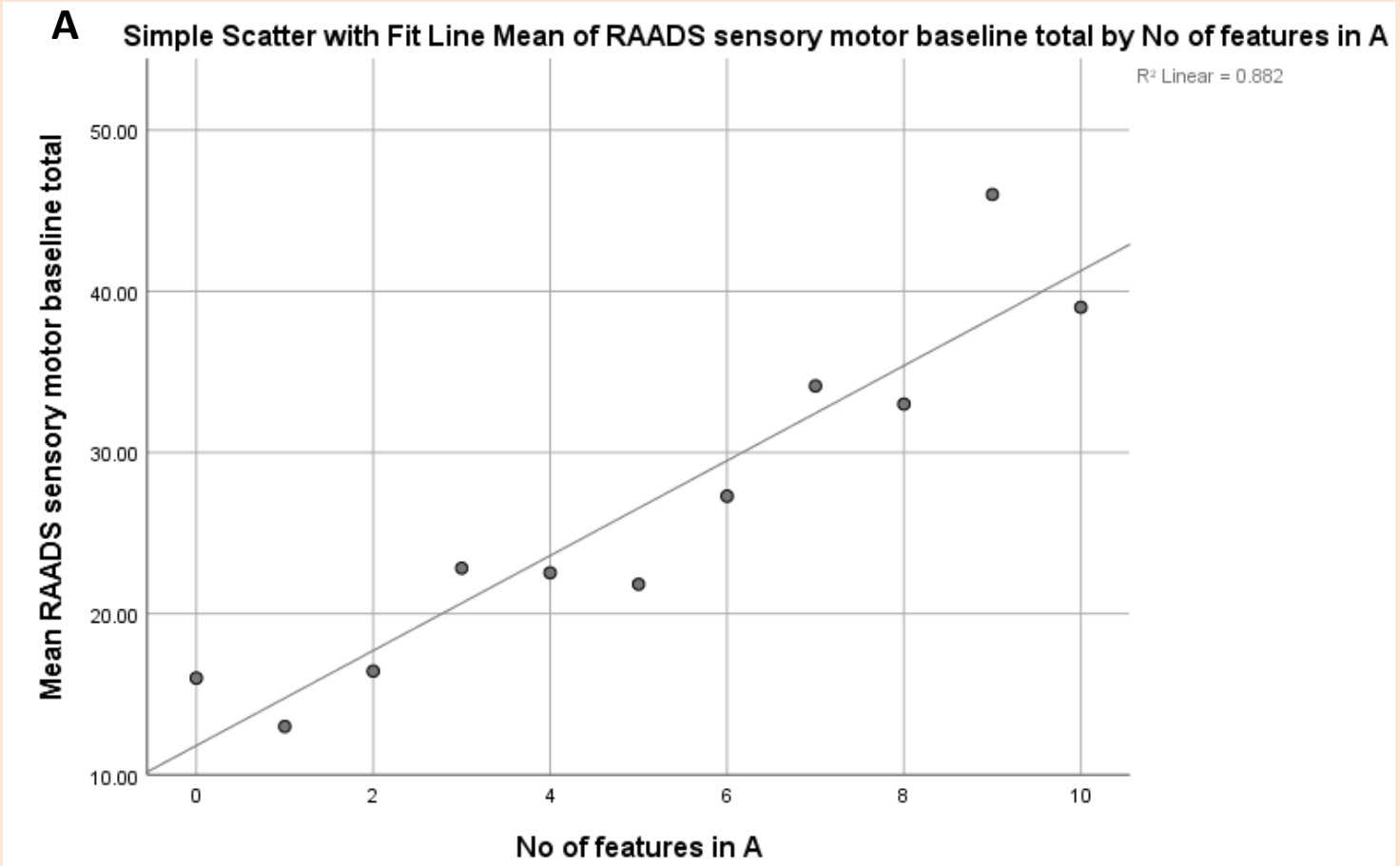
Beighton Score
Error bars represent +/- 1 SEM

- Increased awareness
- Think JH in ND
- Think ND in JH
- Service provision and strategies – ND friendly and accessible?
- Further work – emotional/sensory regulation



Sensory processing – role of variant connective tissue



A: The number of connective tissue features (hEDS Criterion 2A) correlated with RAADS-R sensory/motor score (n=110, *r* = .329, p = .002)

Eccles et al., (in prep)

We need more research into why this relationship exists, more recognition and awareness, and improved access to personalised healthcare.

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Clinical Medicine Journal

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The challenges of chronic pain and fatigue

Jessica A Eccles and Kevin A Davies

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DOI: https://doi.org/10.7861/clinmed.2020-1009

Clin Med January 2021

ABSTRACT

In this review, we explore the challenges of chronic pain and fatigue in clinical practice. Both pain and fatigue are common, troubling and frequently overlapping symptoms, and we describe both the clinical burden and the 'clinical problem'. We explore commonly associated symptoms and possible pathological associations, including variant connective tissue (joint hypermobility), small fibre neuropathy, mast cell activation, dysregulated inflammatory and interoceptive processes, which may inform treatment targets. We suggest a multidisciplinary management approach.

KEYWORDS:

PAIN FATIGUE FIBROMYALGIA HYPERMOBILITY, RHEUMATOLOGY

Clinical burden of chronic pain and fatigue

Further understanding of pain and fatigue is clinically important as they are among the most frequent symptoms reported by patients.[1] When these symptoms are 'persistent' or 'unexplained' they are associated with poorer quality of life and higher costs than other patient groups.[2] They also pose a diagnostic conundrum and have a significant impact on healthcare utilisation costs and significant indirect costs.[3,4]

There is growing interest in associated dysautonomia, for example, postural orthostatic tachycardia syndrome (PoTS) in which the heart rate rises excessively on standing with attendant symptoms including dizziness, light-headedness, fatigue and palpitations. In addition to orthostatic stress, symptoms can be provoked by heat intolerance and can be worse after eating.[24] Such abnormalities of the autonomic nervous system are frequently found in both fibromyalgia and ME/CFS.[25,26]

Long COVID is, at the time of writing, still very poorly understood, however, and there are a number of current centrally-funded research initiatives designed to address (among other things) whether there is objective evidence of chronic nervous system damage (central, peripheral or autonomic) and whether there are specific genetic factors that may pre-dispose an individual to chronic illness after acute infection.

We discuss later the importance of identifying other conditions that may present with chronic fatigue, pain or related symptoms, and this is, of course, no less important in the context of long COVID. Throughout this article we have, however, emphasised the need for a holistic, multi-professional approach to our patients. It is encouraging to hear that the NHS is investing in 40 centres precisely for this purpose. We hope, however, that these centres will not restrict their remit exclusively to the care of long COVID sufferers. Encouraging news on vaccine development may mean that COVID-19 is 'defeated' and long COVID may hopefully be of little clinical importance in 5 years' time. Patients, such as our index case (Patient A), will, on the other hand, always be there.

Design of the study – Stage I

Baseline Screening assessment and group allocation

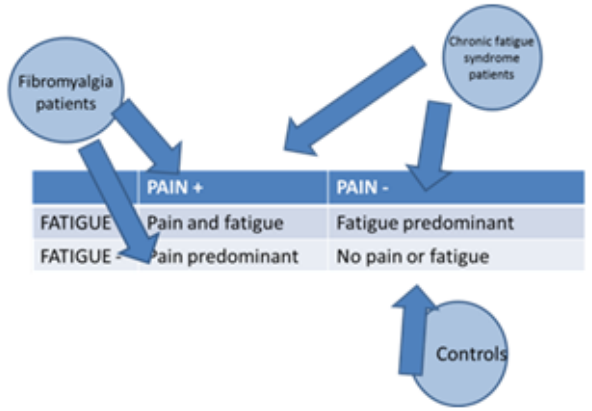
- 25 per group
- Diagnostic assessment of fibromyalgia and ME/CFS
  - via telephone (approx. 30 mins – 1 hour)

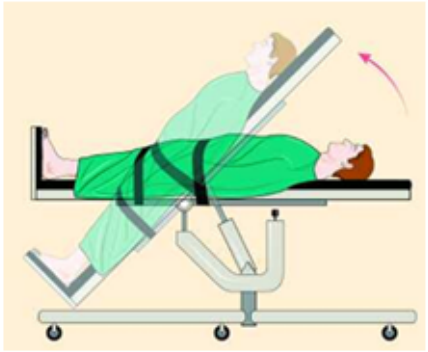
Phase I - Autonomic Challenge
Vascular Lab NIHR CRF/CIRU BSUH

-all participants

- Baseline pain, fatigue, cognitive and autonomic assessment
- Measurement of peripheral markers of inflammation
- Measurement of pain, fatigue, cognition and sensory processing during **sympathetic challenge** (Head Up Tilt)

-- 1 visit (3 hours)





Participants: ME/CFS (Fatigue>Pain), Fibromyalgia (Pain>Fatigue), Controls
Baseline inflammatory markers: CRP and ESR

ISRCTN78820481

Design of the study – Stage II

Phase II – Inflammatory Challenge
Clinical Imaging Sciences Centre, BSMS

-all participants

- Baseline pain, fatigue, cognitive and autonomic assessment
- Baseline peripheral markers of inflammation
- **Inflammatory challenge** (Typhoid vaccination or placebo)
  - Measurement of pain, fatigue, cognition and sensory processing post challenge
  - 3T Neuroimaging: fMRI of cognition and fatigue; qMT structural scan; resting state
  - Peripheral markers of inflammation; measurement of gene expression

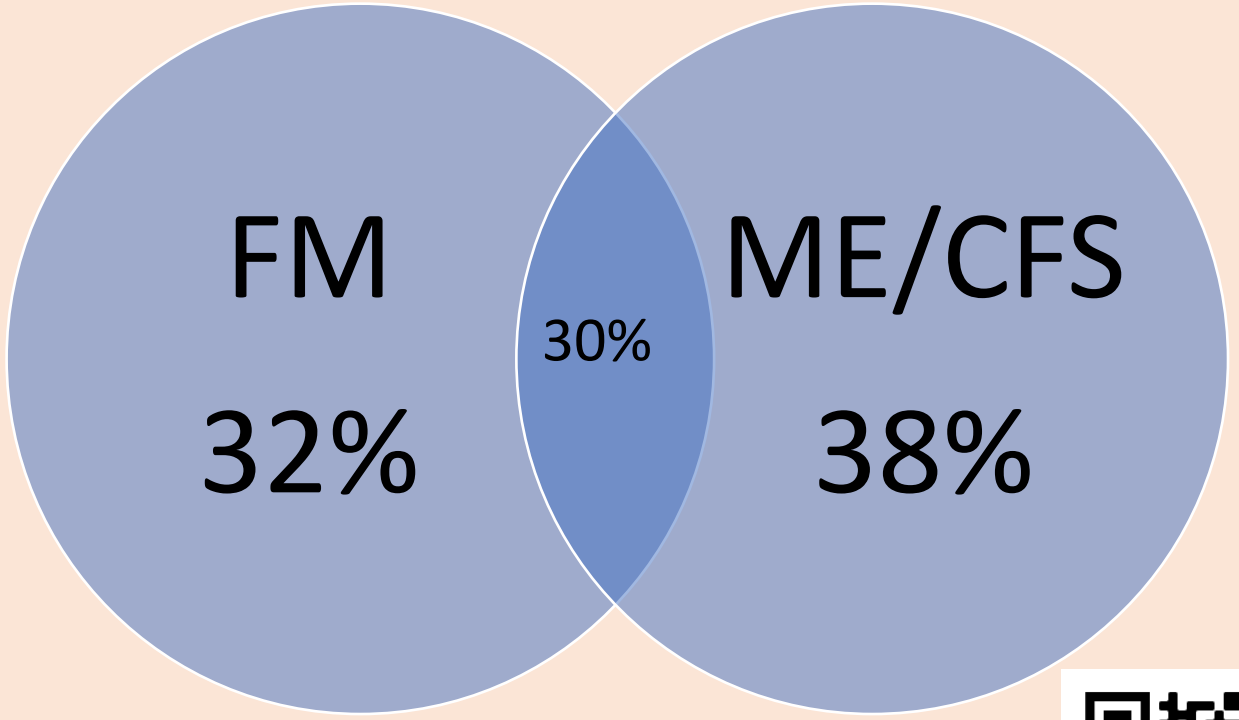
--2 visits (each 3 hours) cross over design (vaccination/placebo)

Participants: ME/CFS (Fatigue>Pain), Fibromyalgia (Pain>Fatigue), Controls
Cytokines: mRNA transcriptomics and individual cytokines (IL-6)

ISRCTN78820481

Results – Classification Eccles et al 2021

- Of the 65 patients, 32% had received a clinical diagnosis of Fibromyalgia; 38% ME/CFS and 30% both diagnoses



Observational Study › Clin Med (Lond). 2021 Jan;21(1):53-58. doi: 10.7861/clinmed.2020-0743.

Beyond bones: The relevance of variants of connective tissue (hypermobility) to fibromyalgia, ME/CFS and controversies surrounding diagnostic classification: an observational study

Jessica A Eccles [1], Beth Thompson [2], Kristy Themelis [2], Marisa L Amato [2], Robyn Stocks [2], Amy Pound [3], Anna-Marie Jones [4], Zdenka Cipinova [5], Lorraine Shah-Goodwin [5], Jean Timeyin [5], Charlotte R Thompson [6], Thomas Batty [7], Neil A Harrison [8], Hugo D Critchley [9], Kevin A Davies [6]

Affiliations + expand

PMID: 33479068 PMCID: PMC7850199 DOI: 10.7861/clinmed.2020-0743

Free PMC article

Abstract

Background: Fibromyalgia and myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) are poorly understood conditions with overlapping symptoms, fuelling debate as to whether they are manifestations of the same spectrum or separate entities. Both are associated with hypermobility, but this remains significantly undiagnosed, despite impact on quality of life.

Objective: We planned to understand the relevance of hypermobility to symptoms in fibromyalgia and ME/CFS.

Method: Sixty-three patient participants presented with a confirmed diagnosis of fibromyalgia and/or ME/CFS; 24 participants were healthy controls. Patients were assessed for symptomatic hypermobility.

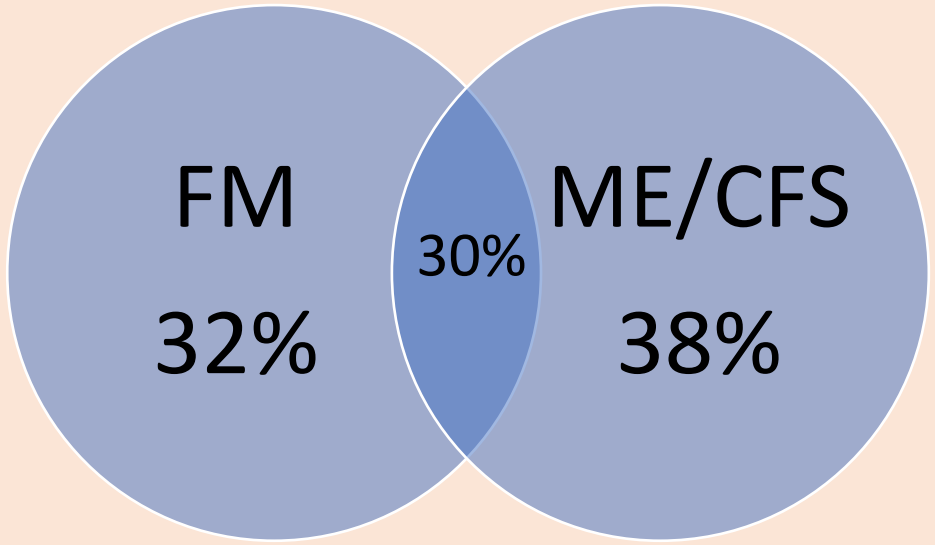
Results: Evaluations showed exceptional overlap in patients between fibromyalgia and ME/CFS, plus 81% met Brighton criteria for hypermobility syndrome (odds ratio 7.08) and 18% met 2017 hypermobile Ehlers-Danlos syndrome (hEDS) criteria. Hypermobility scores significantly predicted symptom levels.

Conclusion: Symptomatic hypermobility is particularly relevant to fibromyalgia and ME/CFS, and our findings highlight high rates of mis-/underdiagnosis. These poorly understood conditions have a considerable impact on quality of life and our observations have implications for diagnosis and treatment targets.

Keywords: ME/CFS; fatigue; fibromyalgia; hypermobility; pain.

Results – Classification Eccles et al 2021

- Of the 65 patients, 32% had received a clinical diagnosis of Fibromyalgia; 38% ME/CFS and 30% both diagnoses



89% met ACR diagnostic criteria for Fibromyalgia
94% Canadian Criteria for ME/CFS
97% Fukada Criteria for ME/CFS

Results – Classification Eccles et al 2021

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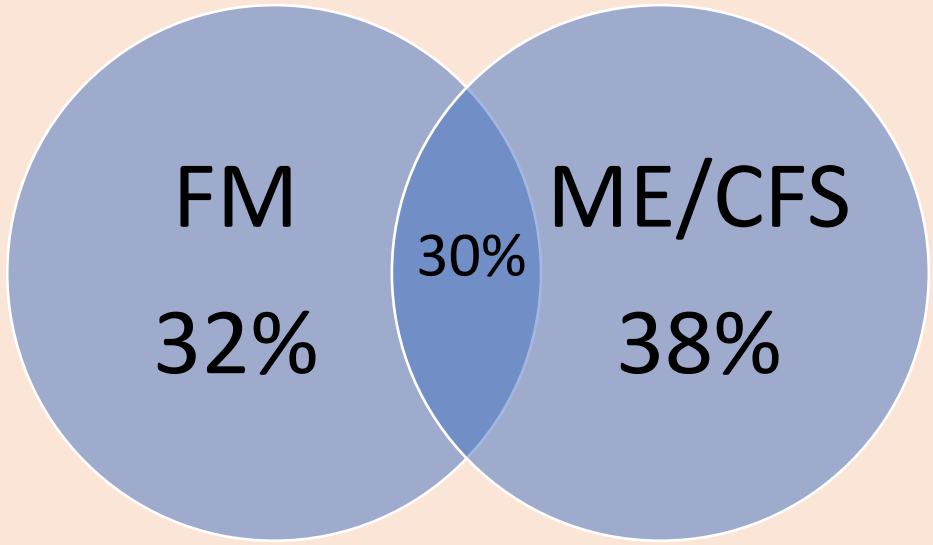

Brighton Criteria for JHS: 81% patients and 37.5% healthy controls

hEDS Criteria: 18% of patients and 8% controls

89% met ACR diagnostic criteria for fibromyalgia
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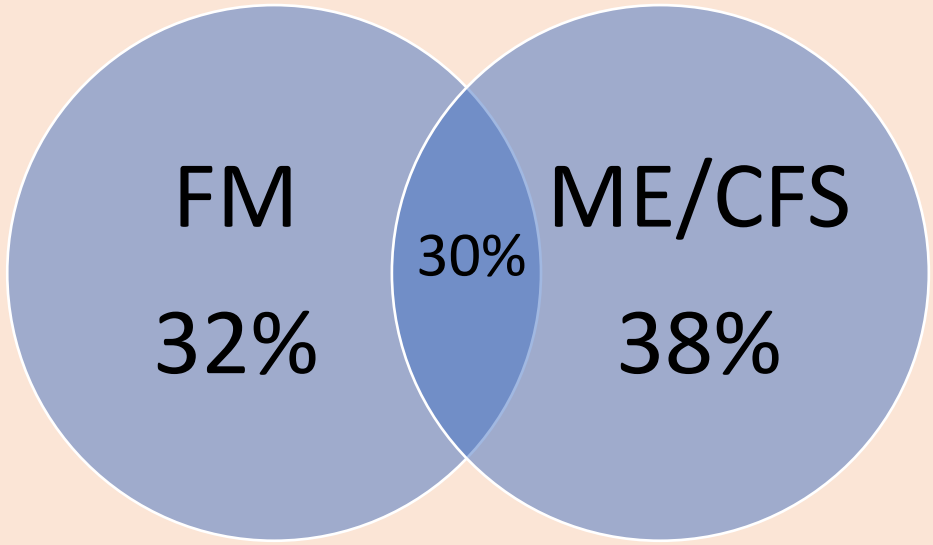


89% met ACR diagnostic criteria for fibromyalgia
94% Canadian Criteria for ME/CFS
97% Fukada Criteria for ME/CFS

Brighton Criteria for JHS: 81% patients and 37.5% healthy controls
hEDS Criteria: 18% of patients and 8% controls
Rarely recognised

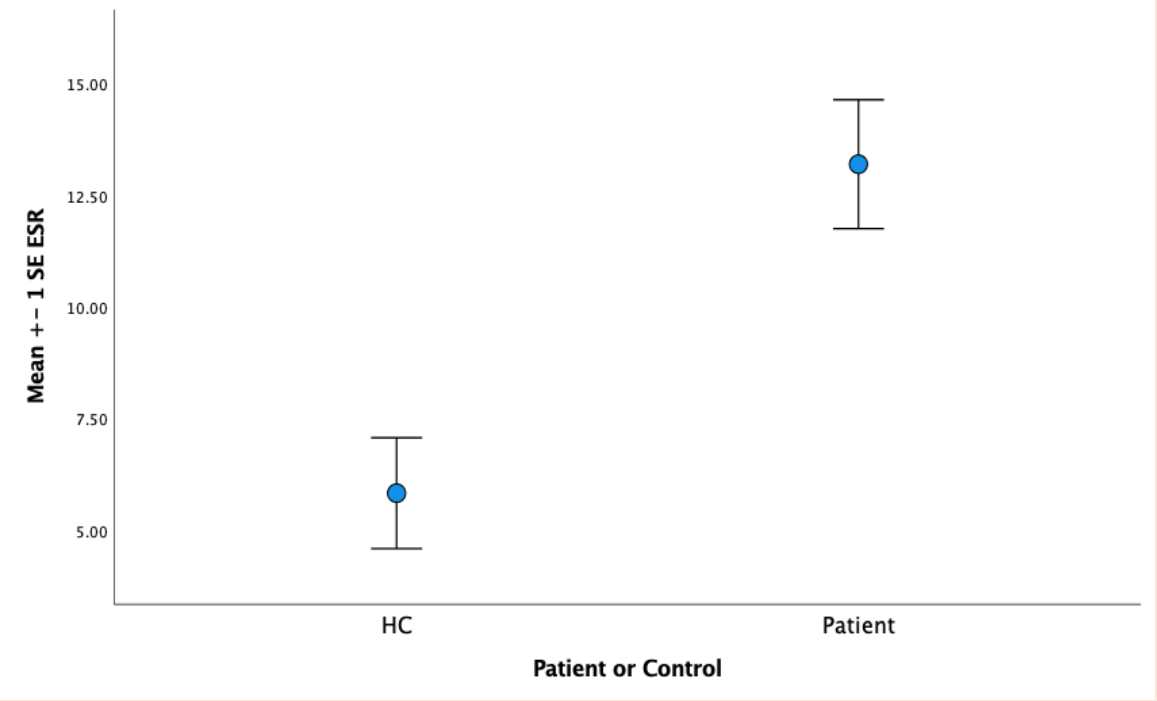
The historical, rather than current Beighton score correlated with:

- Fatigue Impact (p=0.028)
- Total pain reported on the McGill Pain Questionnaire (short form), (p=0.03)
- Widespread Pain Index (derived from ACR diagnostic criteria) (p=0.01)
- ACR symptom severity (p=0.01)
- interoceptive sensibility (p=0.02)
- Mental Clutter (p=0.043)

Markers of baseline inflammation in ME/CFS and fibromyalgia

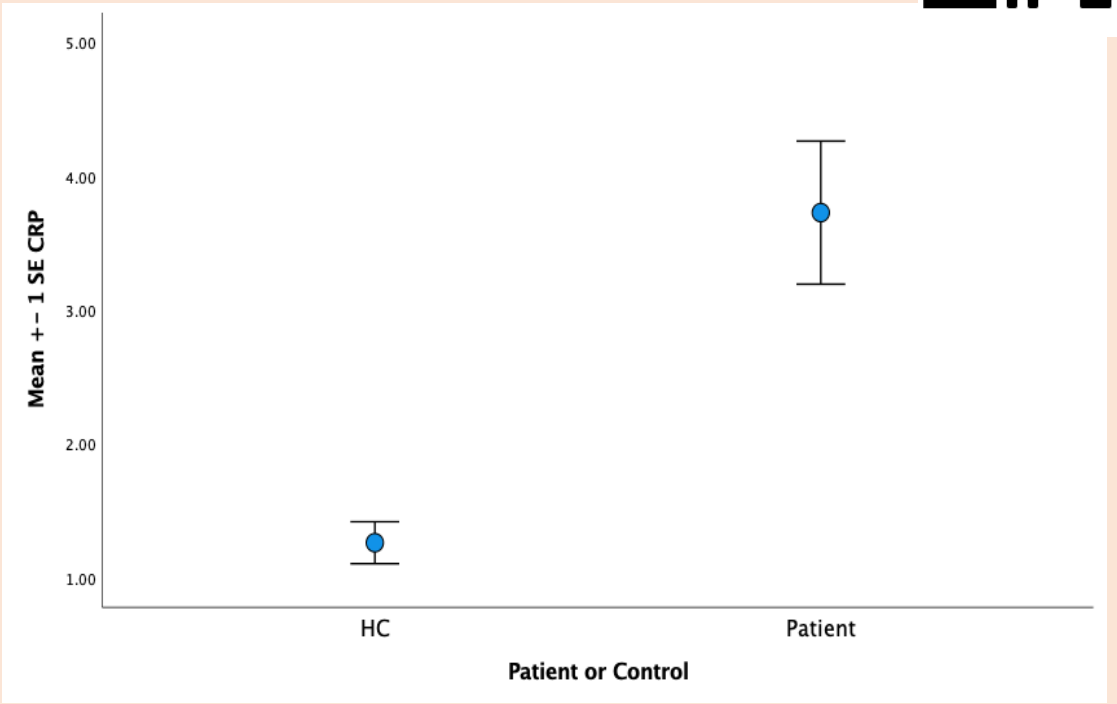
- Traditionally thought that ME/CFS and fibromyalgia non-inflammatory

ESR



There was a higher ESR in patients (mean: 13.20, SEM: 1.45, n=59) compared to controls (5.83, SEM: 1.24, n=23). *Mann-Whitney (MWU 1015.5, Wilcoxon W= 2785.5, p= 0.000)*

CRP



There was a difference in CRP between patients (mean: 3.73, SEM: 0.53, n=60) compared to controls (mean: 1.26, SEM: 0.157, n=23). *Mann-Whitney (MWU 991, Wilcoxon W= 2821, p=0.001)*

Eccles et al 2023; in prep

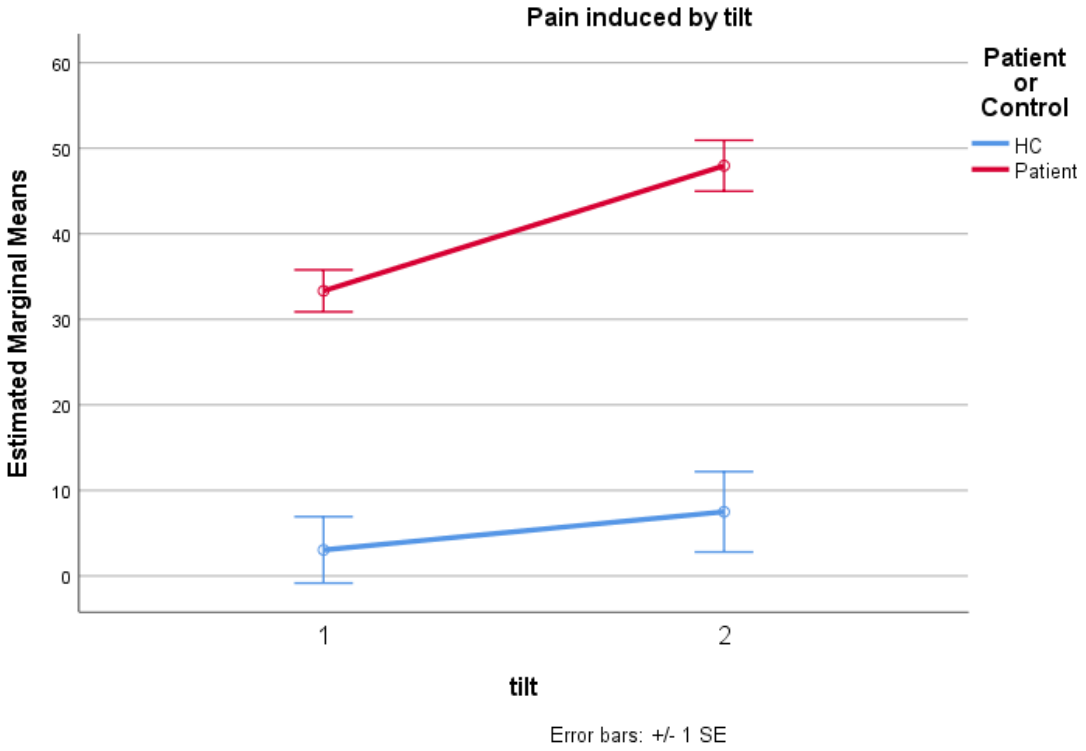
Markers of baseline inflammation in ME/CFS and fibromyalgia

- Traditionally thought that ME/CFS and fibromyalgia non-inflammatory
- Adjusting BMI, age and gender
  - ESR significantly predicts fatigue severity and pain level including cog fatigue and mental clutter
  - CRP significantly predicts fatigue severity and pain level
  - ESR mediates relationship between being and patient and cog fatigue impact at rest

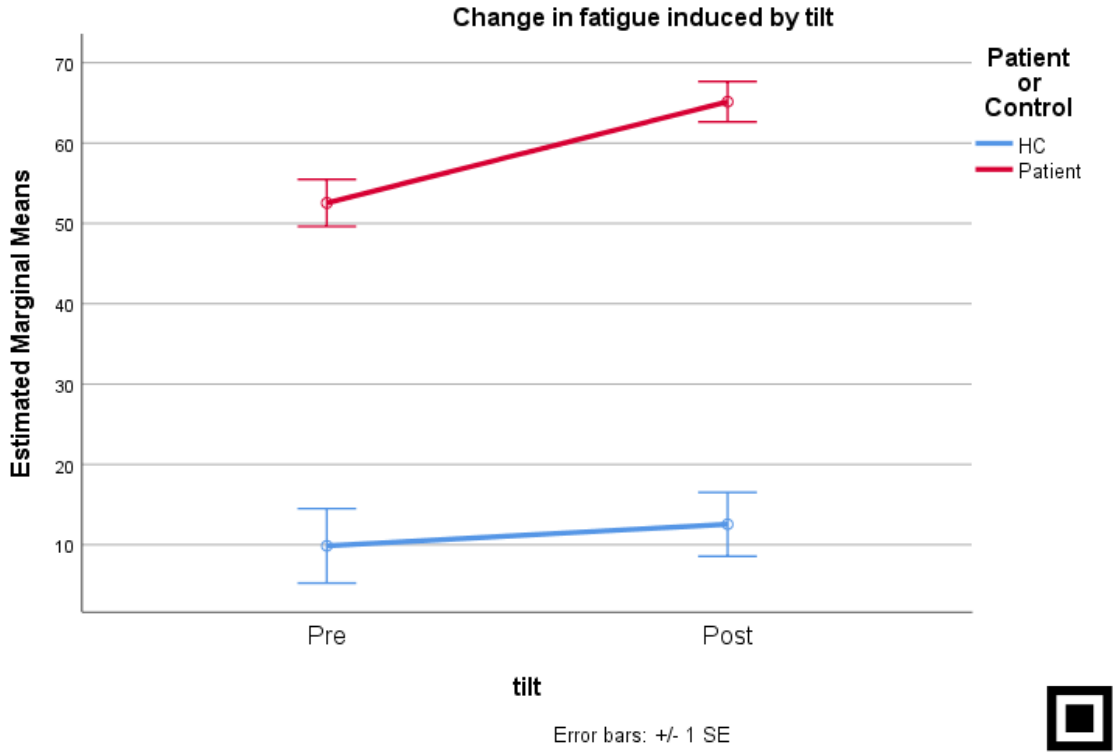
Eccles et al 2023; in prep

Autonomic induced change in pain and fatigue

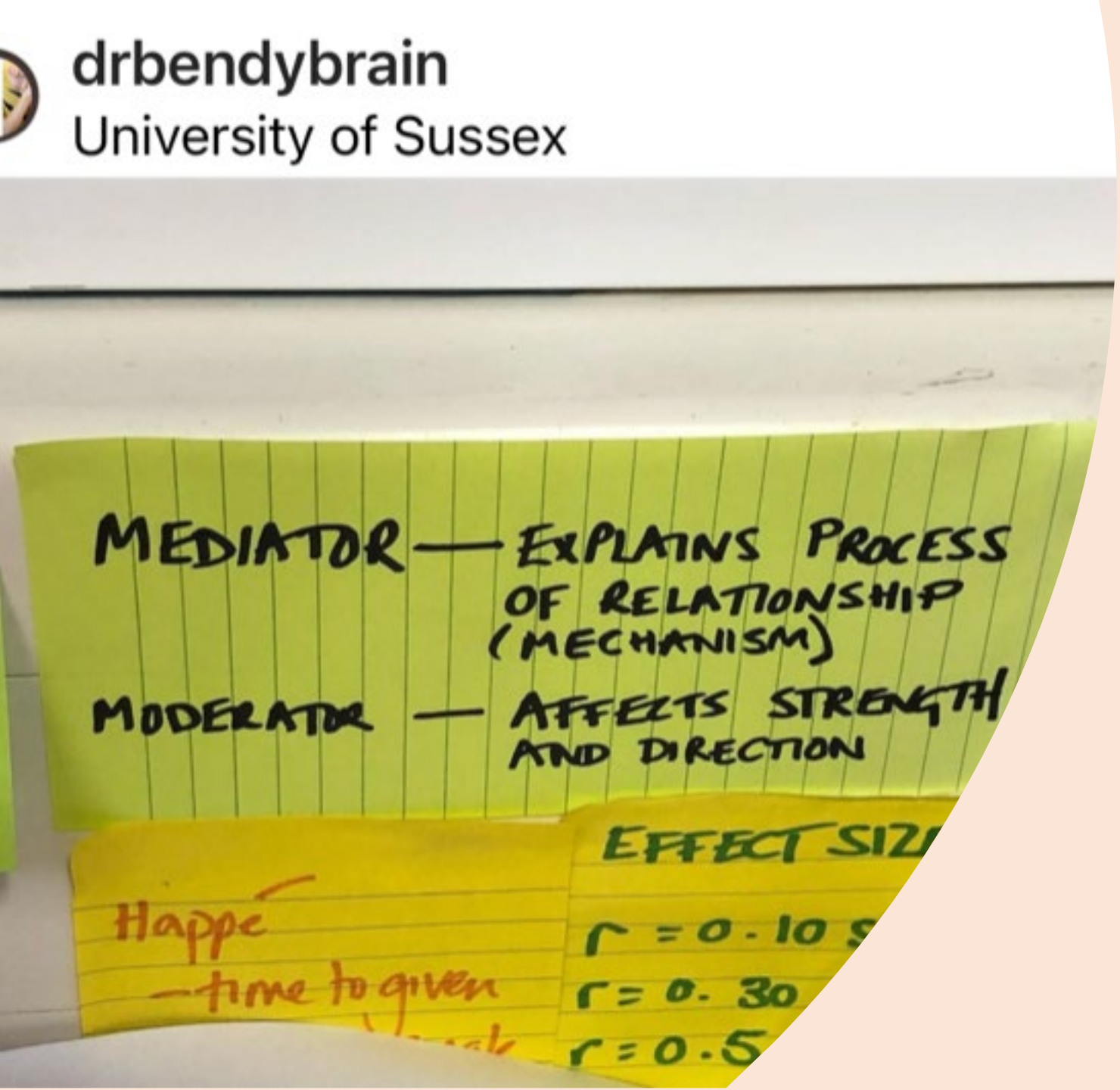
Pain level (VAS) induced by tilt, p=0.005



Fatigue level (VAS) induced by tilt, p<0.001

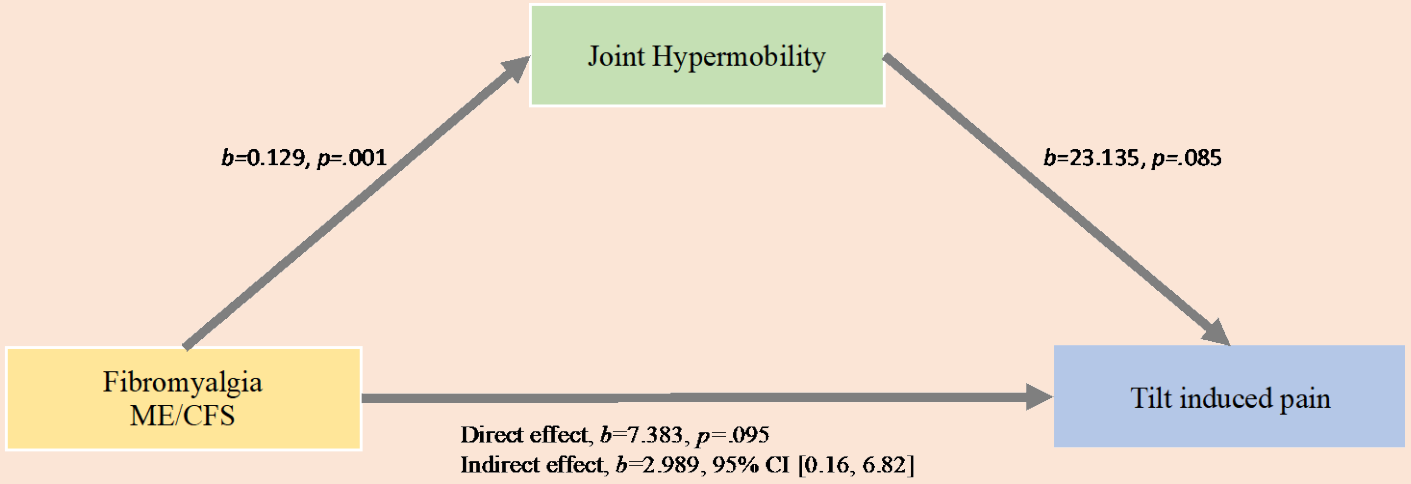


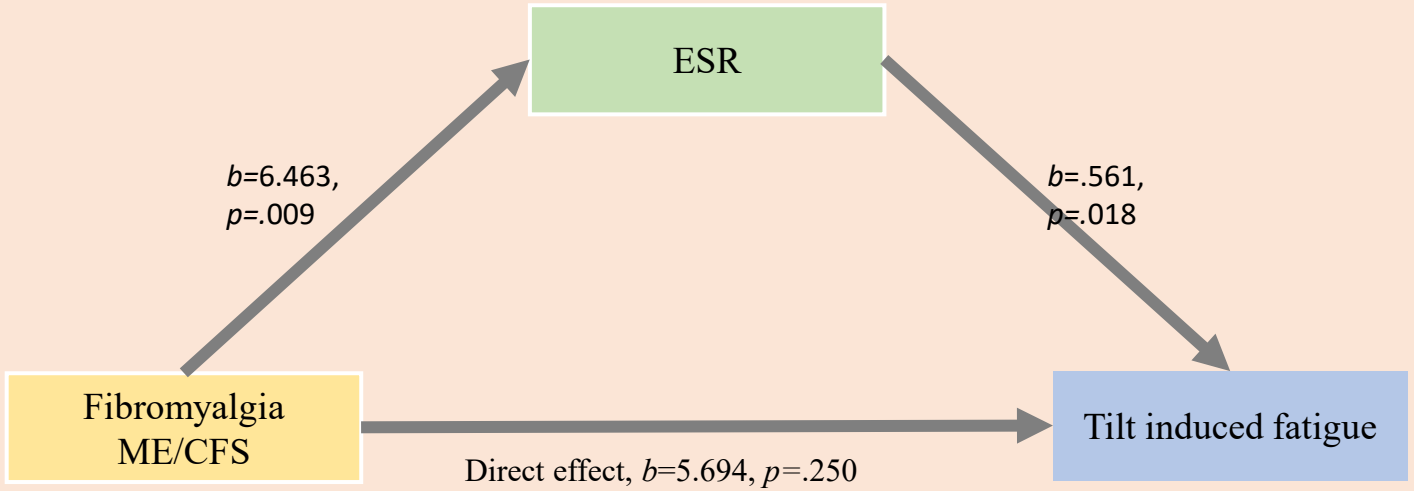
No change in pain *sensitivity* (PPT) induced by tilt



Association to mechanism

Autonomic induced change in pain and fatigue - mechanisms

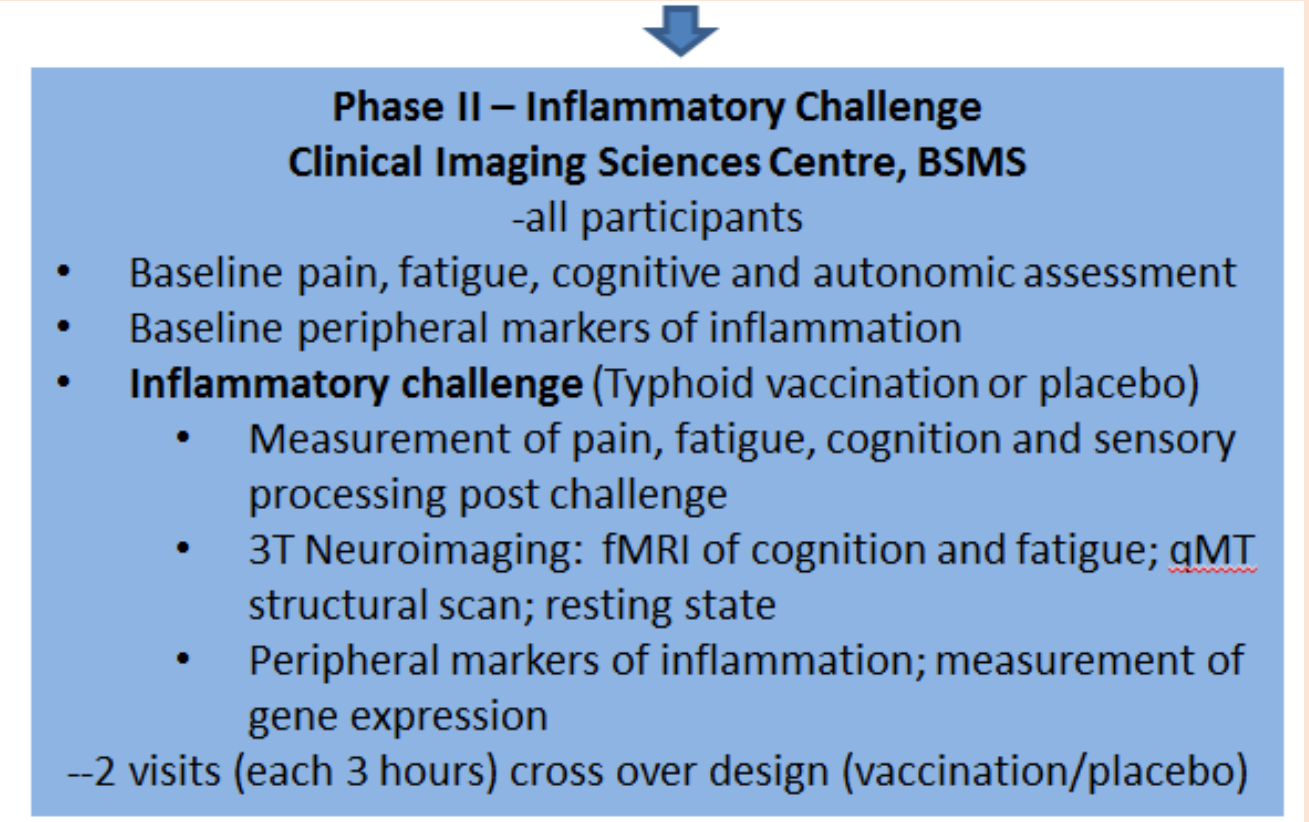




Eccles et al., in prep 22

Similar findings inflamm induced pain/fatigue

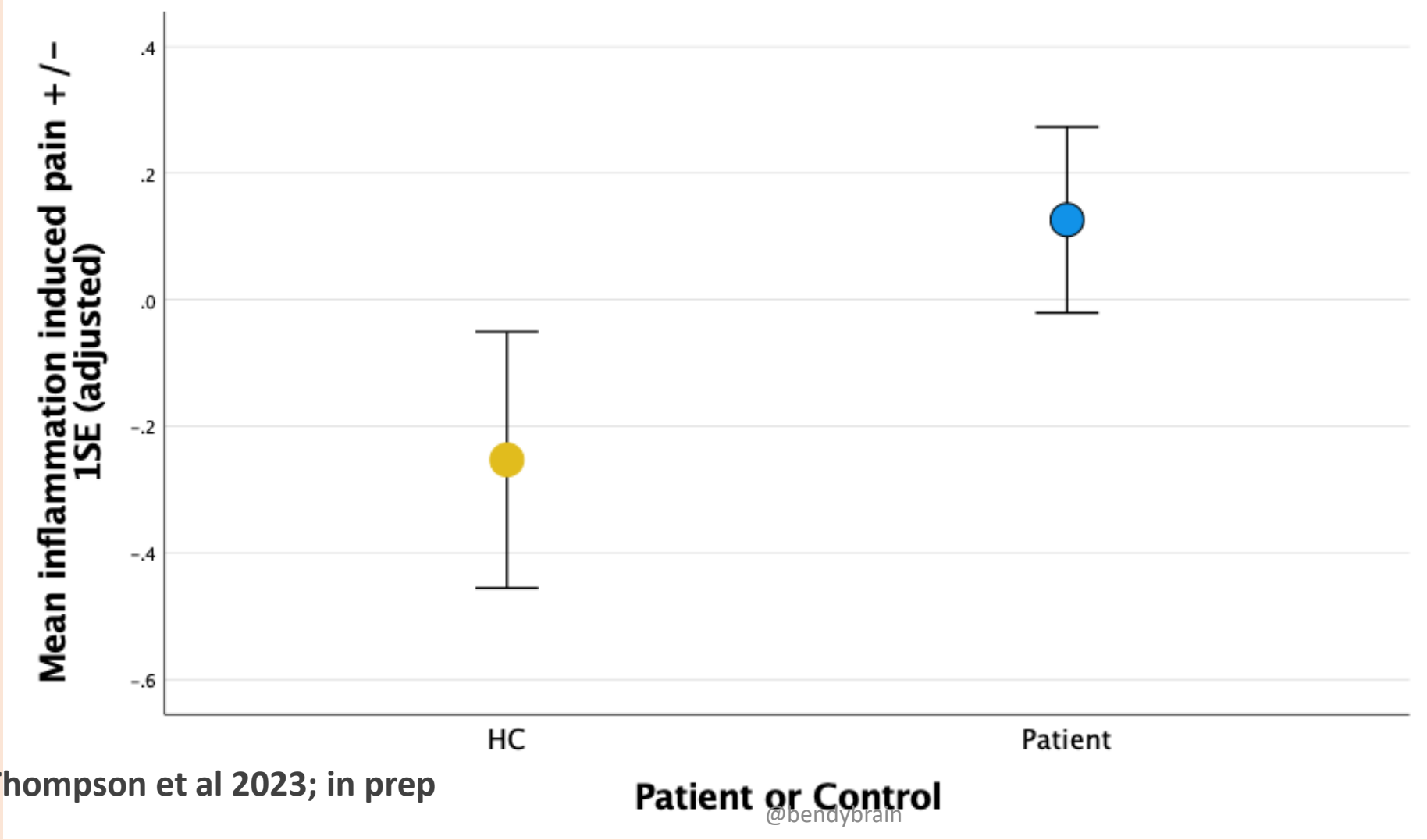
Design of the study – Stage II



Participants: ME/CFS (Fatigue>Pain), Fibromyalgia (Pain>Fatigue), Controls
Cytokines: mRNA transcriptomics and individual cytokines (IL-6)

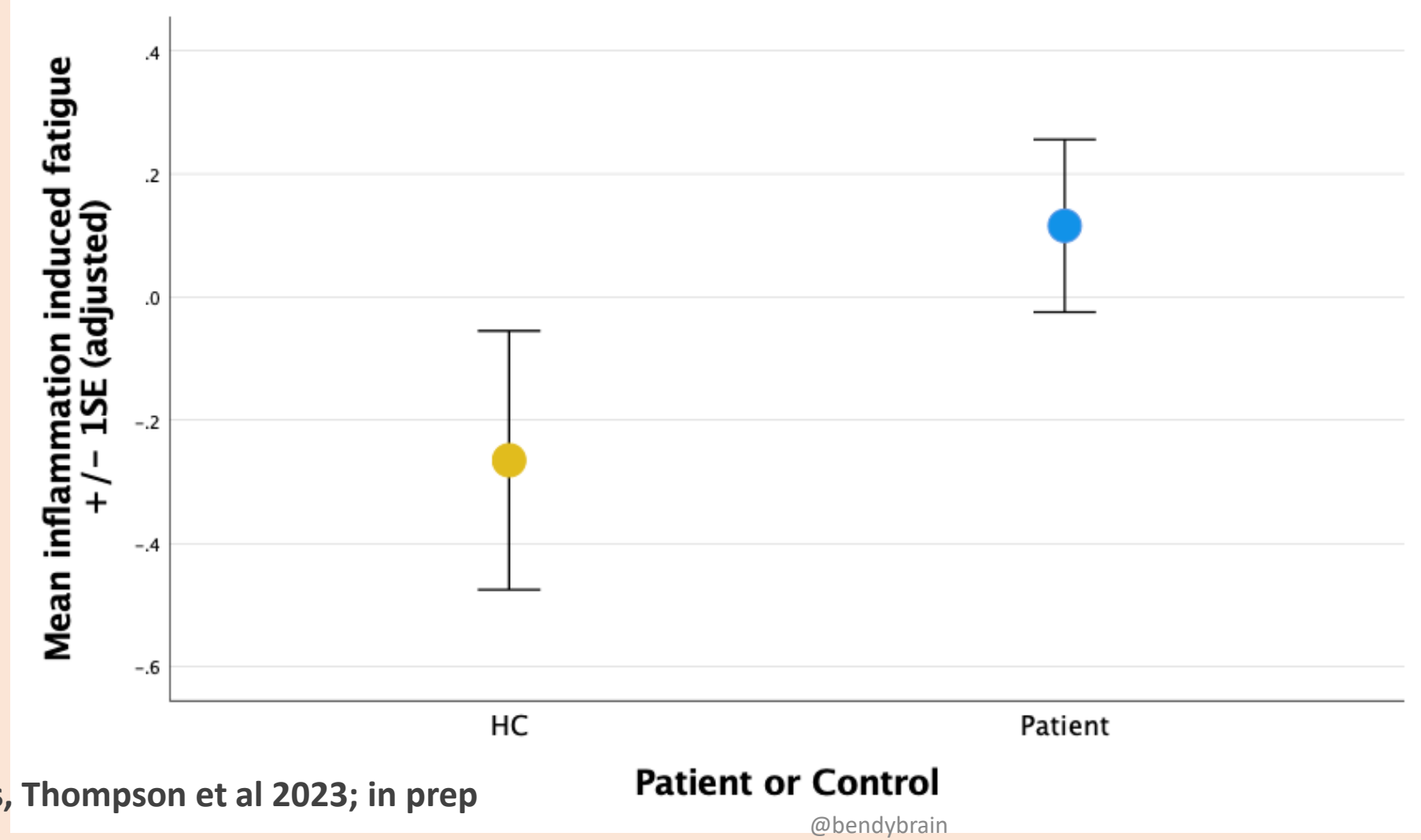
ISRCTN78820481

Inflammation induced pain



Eccles, Thompson et al 2023; in prep

Inflammation induced fatigue



Eccles, Thompson et al 2023; in prep

nature reviews rheumatology

Published: 12 March 2013

Arachnodactyly—a key to diagnosing heritable disorders of connective tissue

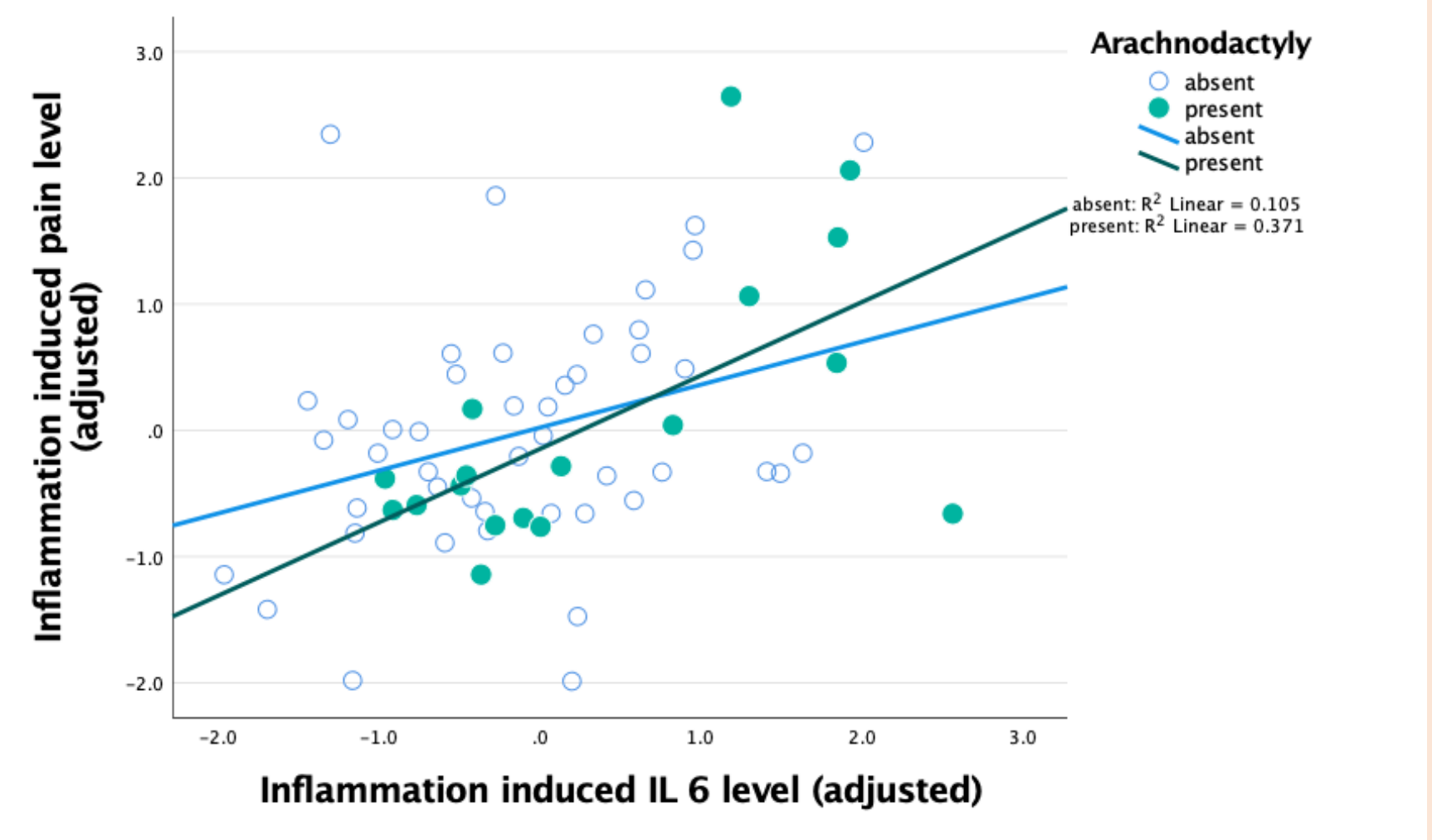
Rodney Grahame & Alan J. Hakim

Nature Reviews Rheumatology **9**, 358–364 (2013) | Cite this article

Abstract

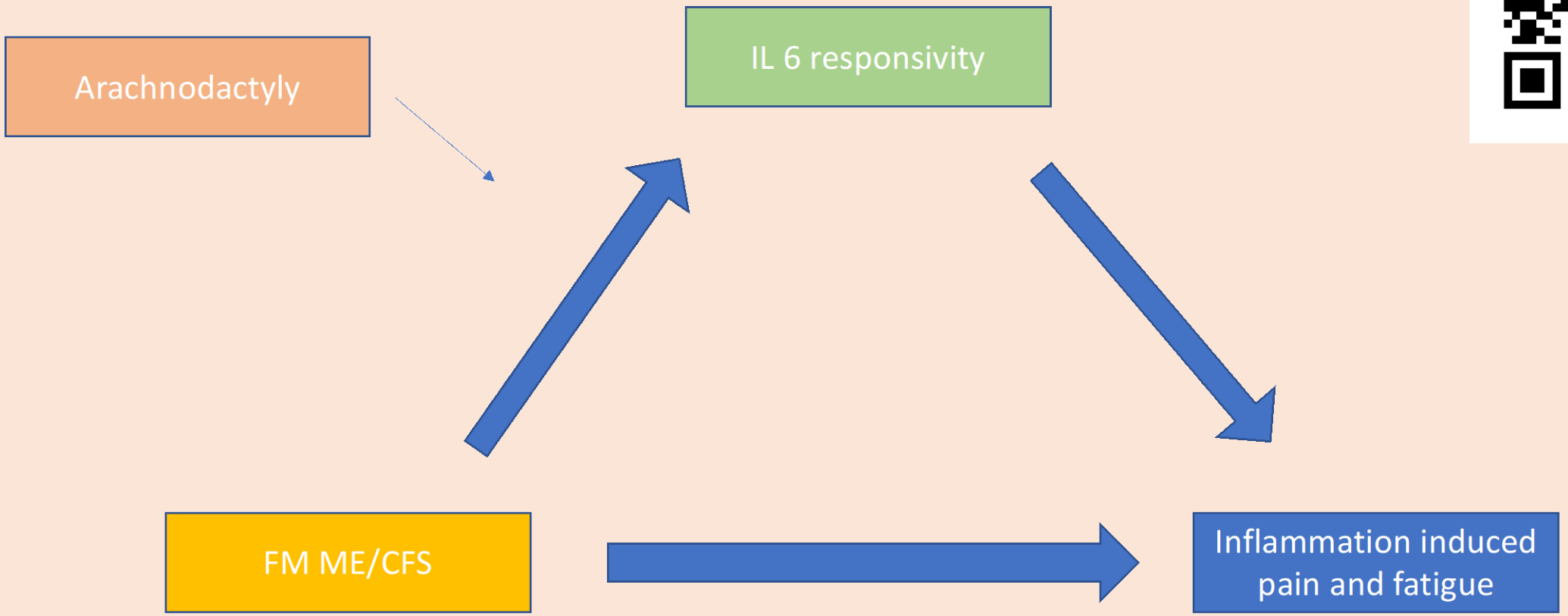
Arachnodactyly literally means spidery fingers, and describes the long, slender fingers typical of patients with Marfan syndrome (MFS). Many clinicians regard arachnodactyly as pathognomonic of MFS; however, this view is misleading as arachnodactyly is a key element of the marfanoid habitus, which is present in several heritable disorders of connective tissue (HDCTs). Other features of the marfanoid habitus include long hands and feet, increased skin stretch, joint hypermobility and characteristic changes in the physiology of the pectum.

IL6 responsivity



Eccles, Thompson et al 2023; in prep

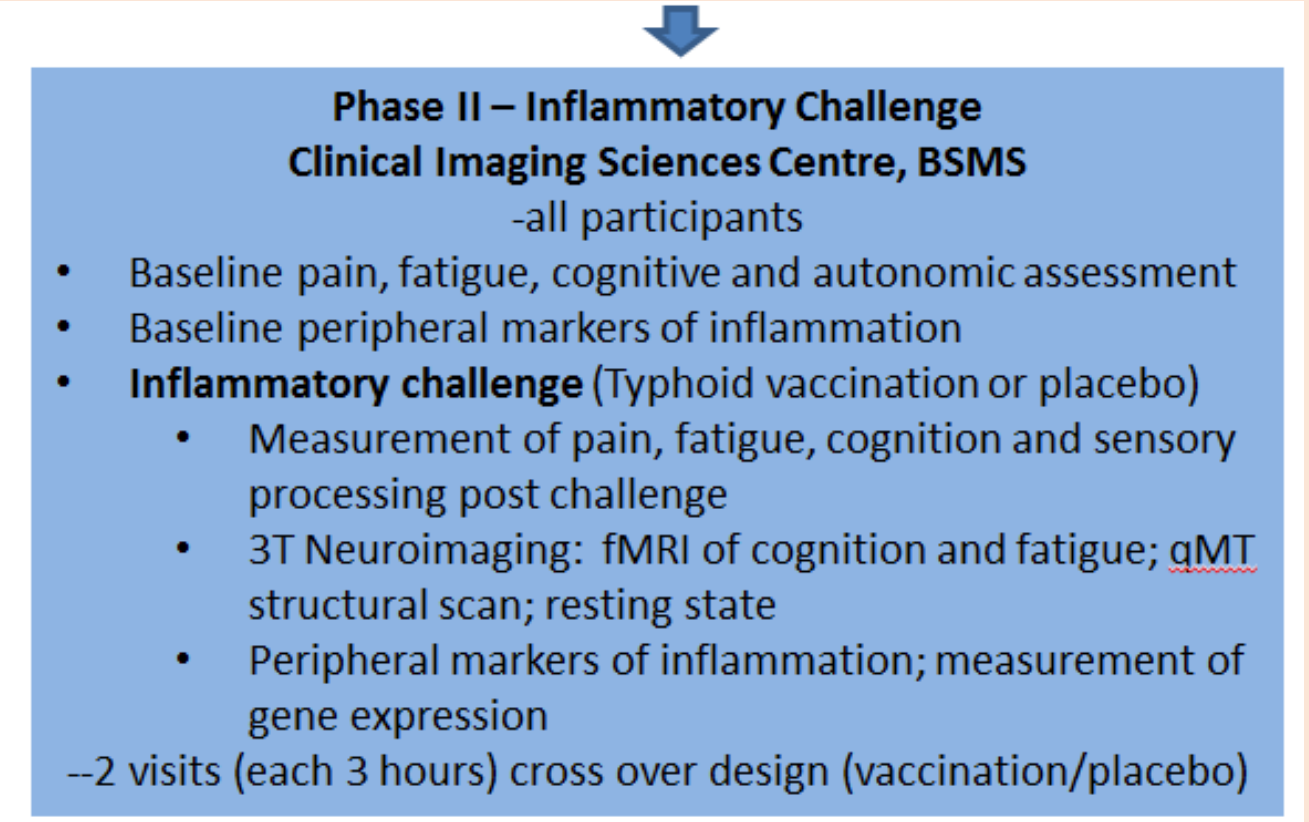
Results



IL6 responsivity links fibromyalgia and ME/CFS to increased inflammation induced pain and fatigue in the presence of arachnodactyly

Eccles, Thompson et al 2023; in prep

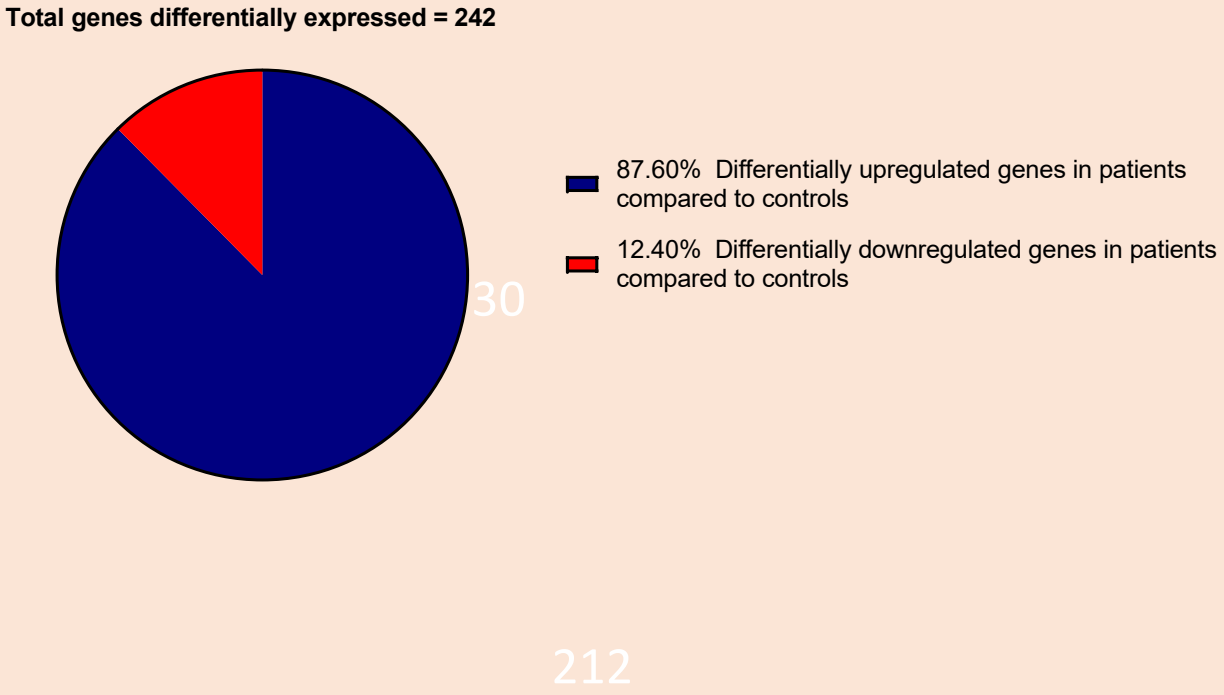
Design of the study – Stage II



Participants: ME/CFS (Fatigue>Pain), Fibromyalgia (Pain>Fatigue), Controls
Cytokines: mRNA transcriptomics and individual cytokines (IL-6)

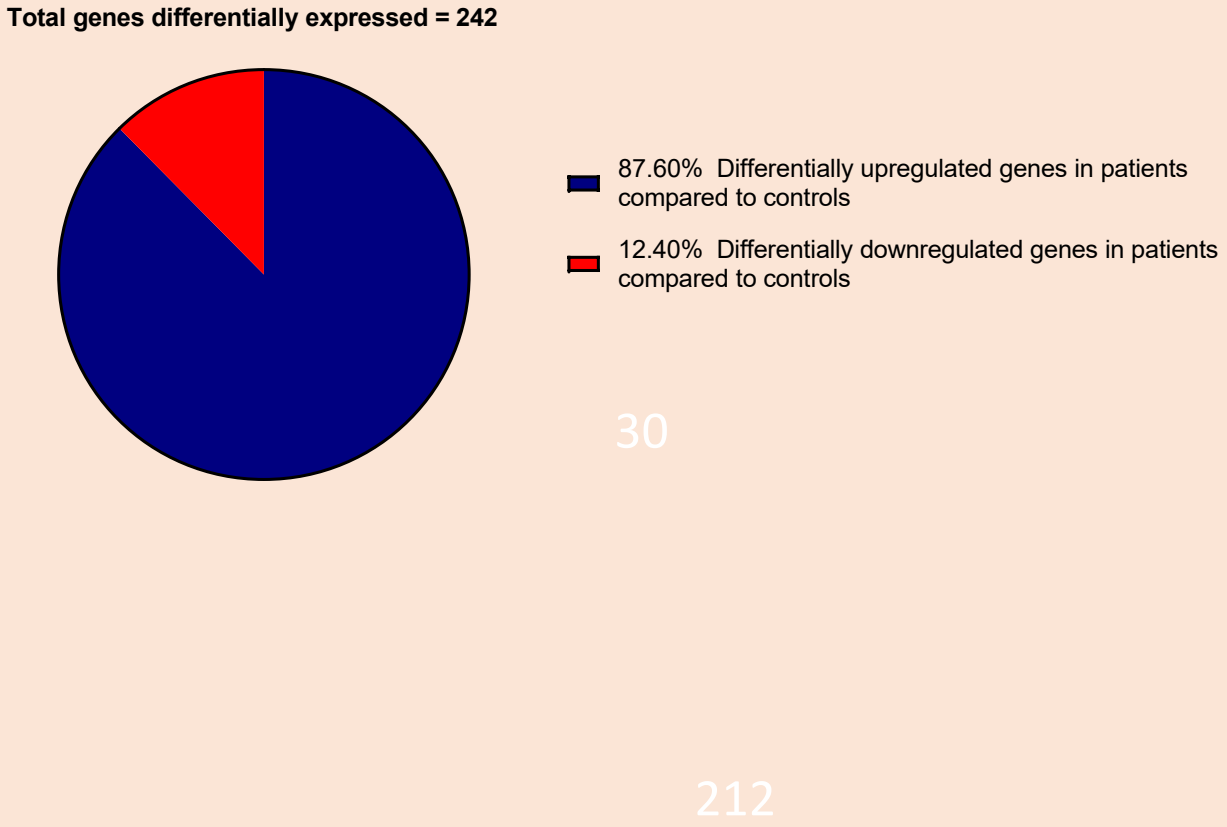
ISRCTN78820481

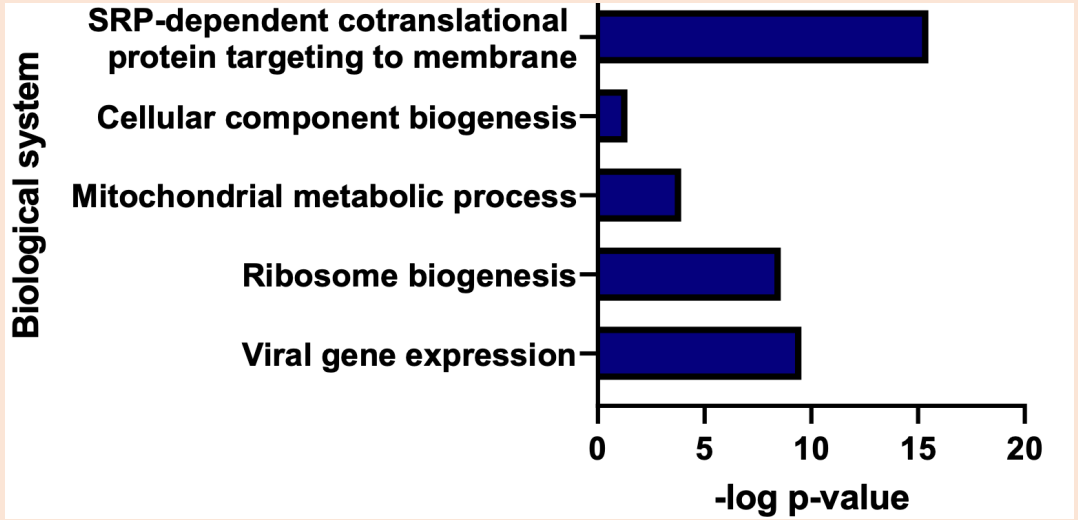
Differentially expressed genes at baseline between patients and controls



Amato et al 2023; in prep

Differentially expressed genes at baseline between patients and controls





Amato et al 2023; in prep

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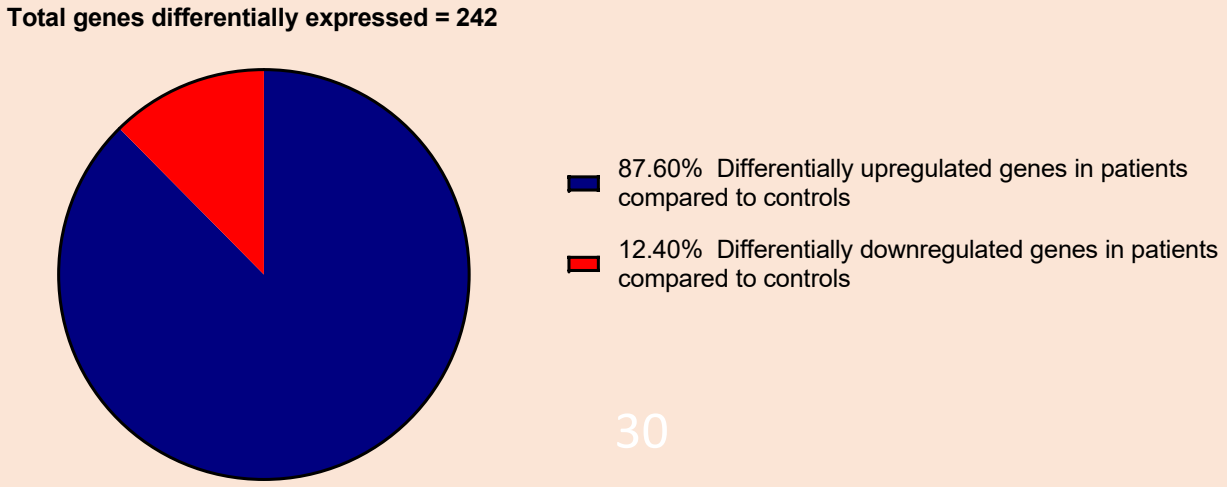

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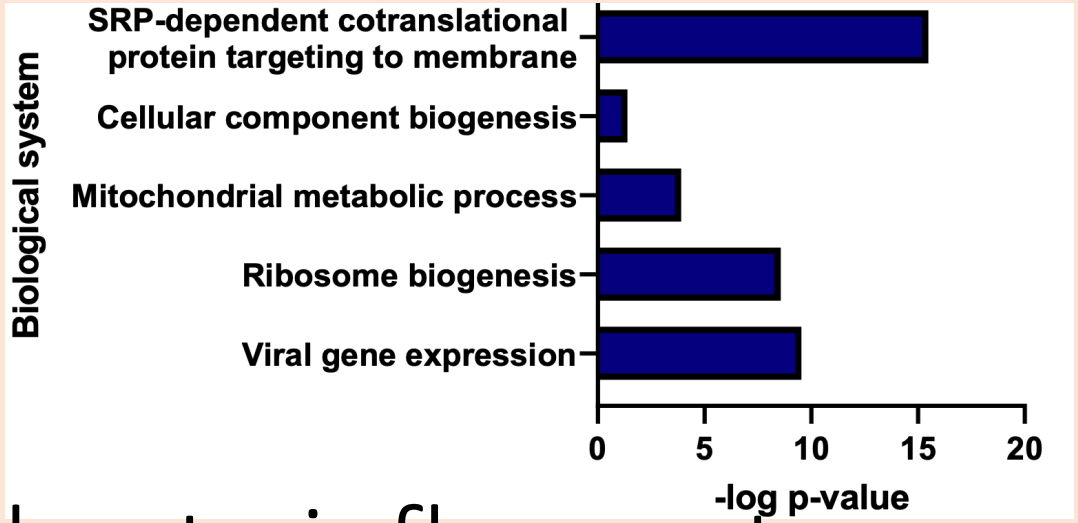
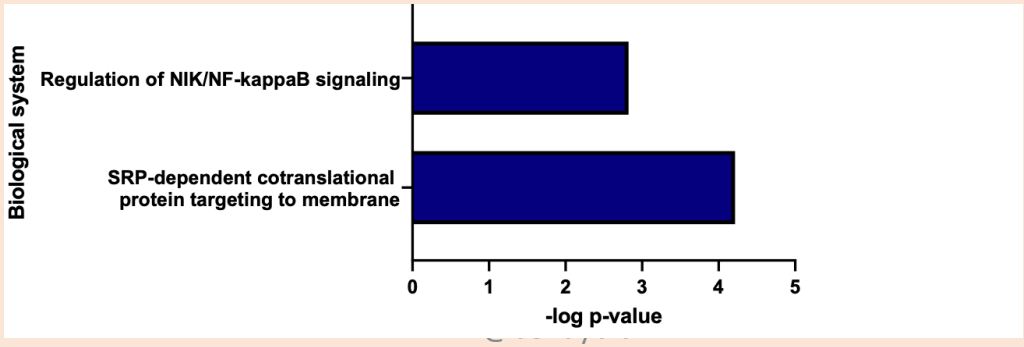


Upregulated in patients due to inflammatory challenge



Amato et al 2023; in prep

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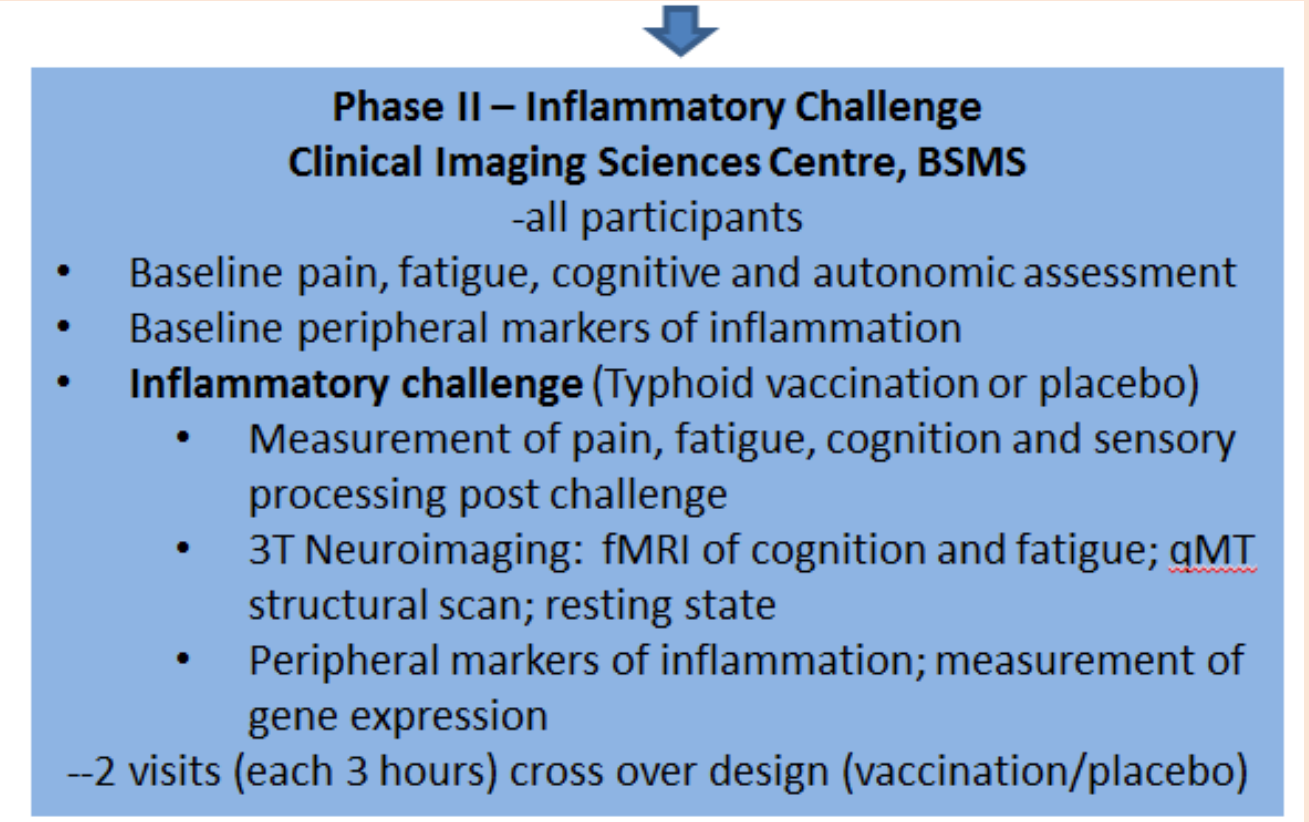
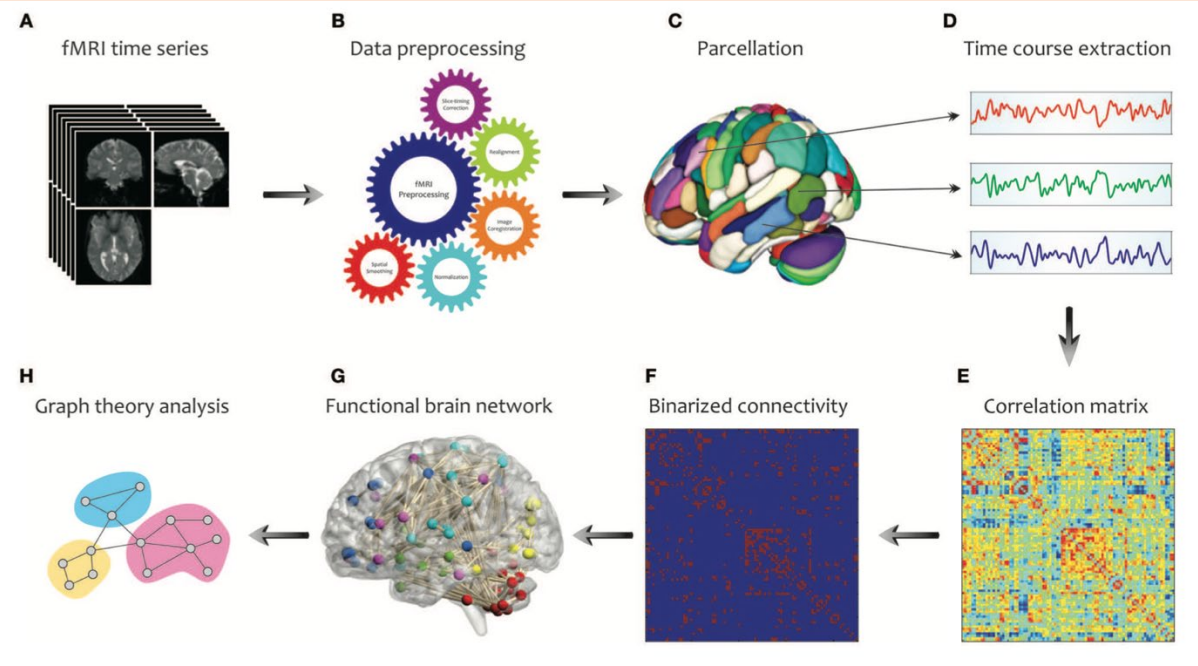


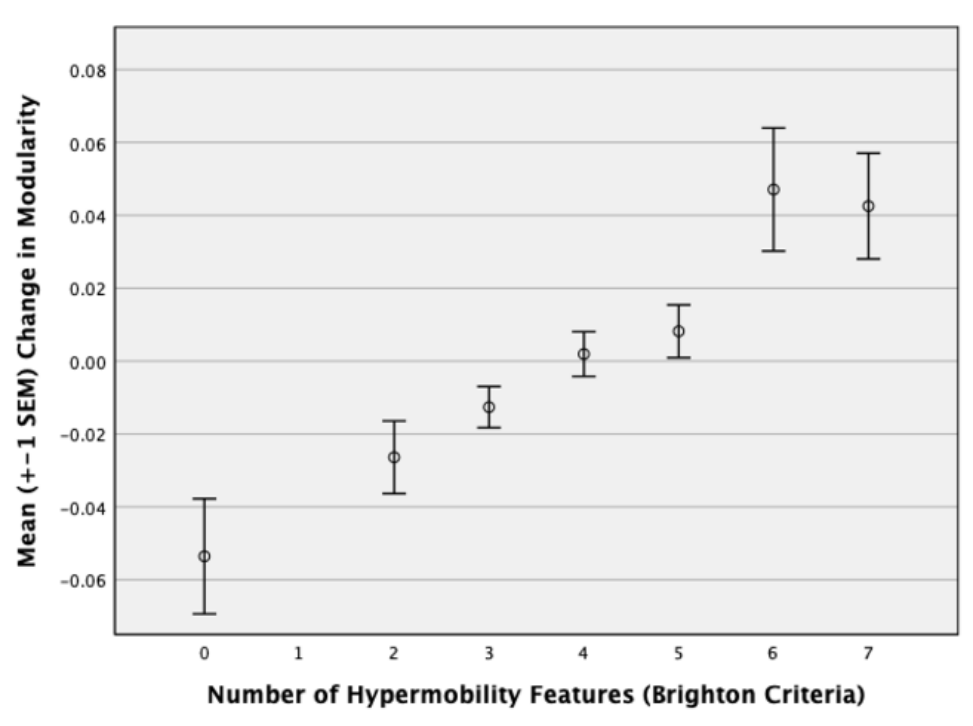
Participants: ME/CFS (Fatigue>Pain), Fibromyalgia (Pain>Fatigue), Controls
Cytokines: mRNA transcriptomics and individual cytokines (IL-6)

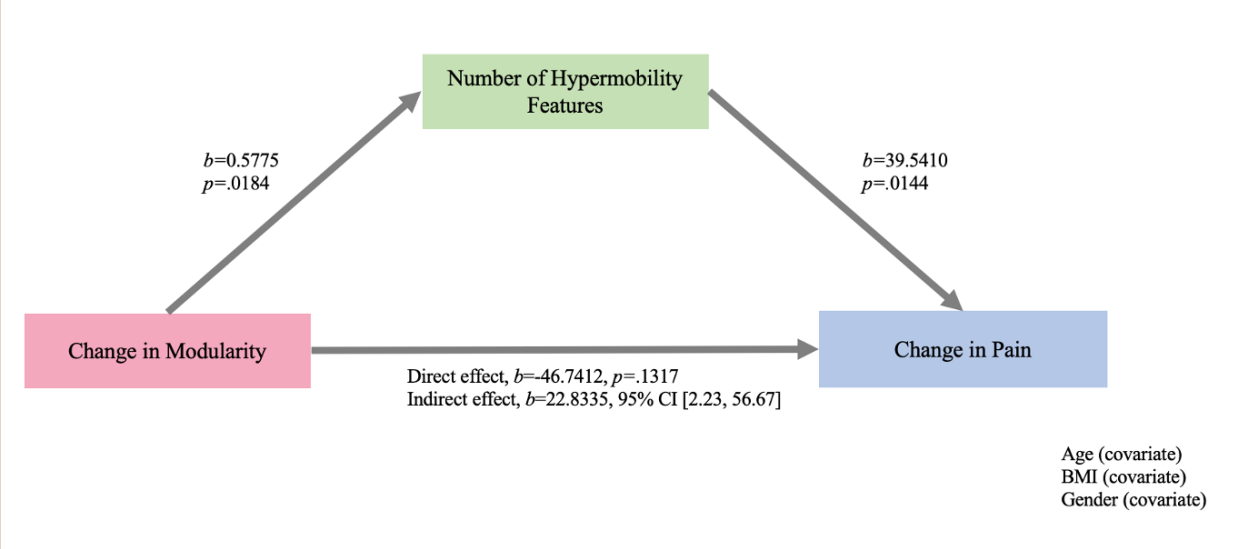
ISRCTN78820481

Brain network response



Brain network response to inflammation





Torok, Sherrill et al 2023; in prep

Dr Ben Towler

Dr Sam Sherrill

Dr Harriet Sharp

Dr Charlotte Thompson

Dr Kristy Themelis

Marisa Amato

Regina Torok

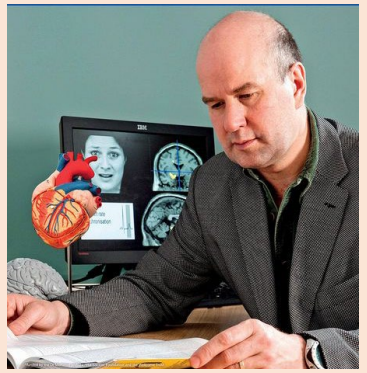
It takes a team

Prof Sarah Newbury

Dr Chris Racey

Dr Lisa Quadt

Prof Kevin Davies



Prof Hugo Critchley

Prof Mara Cercignani

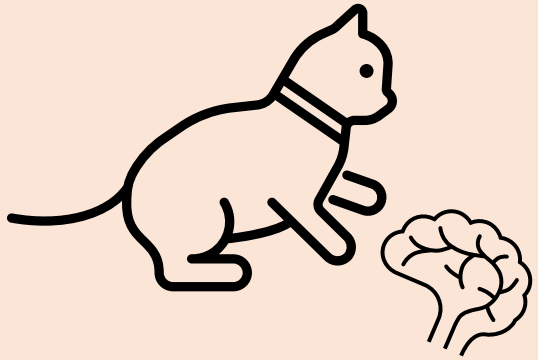
Prof Neil Harrison

The complex connection between neurodivergence and chronic health conditions

Dr Lisa Quadt
Research Fellow

@bendybrain

SN Seed Fund



Neurovisceral Characteristics across the spectrum
(NeuroCats)

Planting the seeds to investigate neural, autonomic, and sensory profiles in neurodivergent adults

Aims

- Estimate prevalence of neurodivergence in complex chronic conditions, e.g. chronic pain and fatigue
- Investigate whether risk factors such as variant connective tissue plays a role
- Goal is to start to identify transdiagnostic patterns that can then lead to changes in diagnostic practice

Quadt…Eccles; in prep

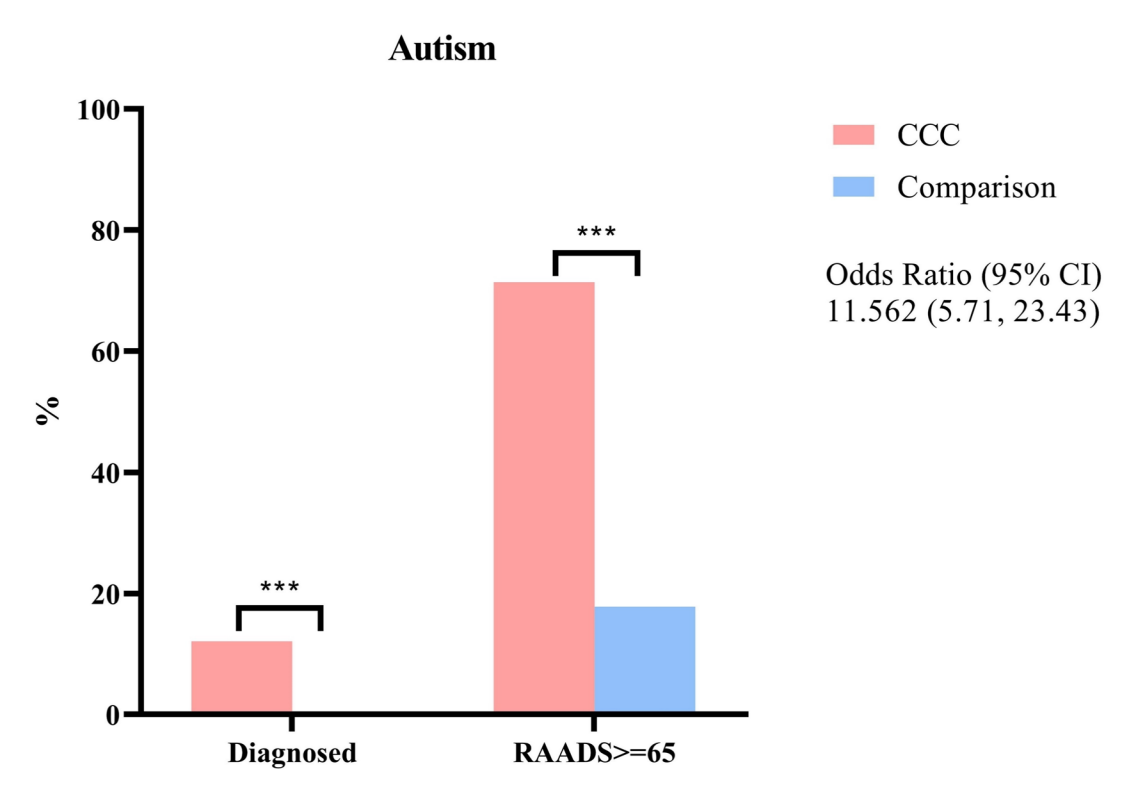
Design

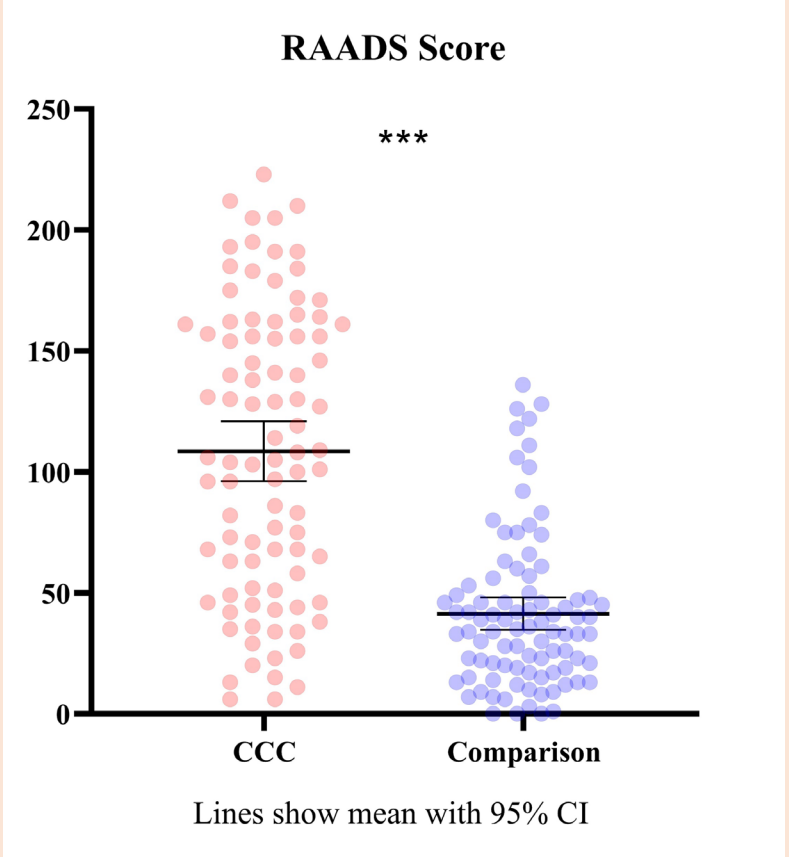
- Online Survey
  - 91 participants with CCCs, 91 matched participants without CCCs (exclusion of all physical and mental health conditions other than depression/anxiety)
- Measures
  - **Ritvo Asperger and Autism Diagnostic Scale (RAADS)**
  - **Wender Utah ADHD Rating Scale (WURS)**

Quadt…Eccles; in prep

UNPUBLISHED DATA – DO NOT SHARE, COPY, DISTRIBUTE

Prevalence of likely autism





Quadt…Eccles; in prep

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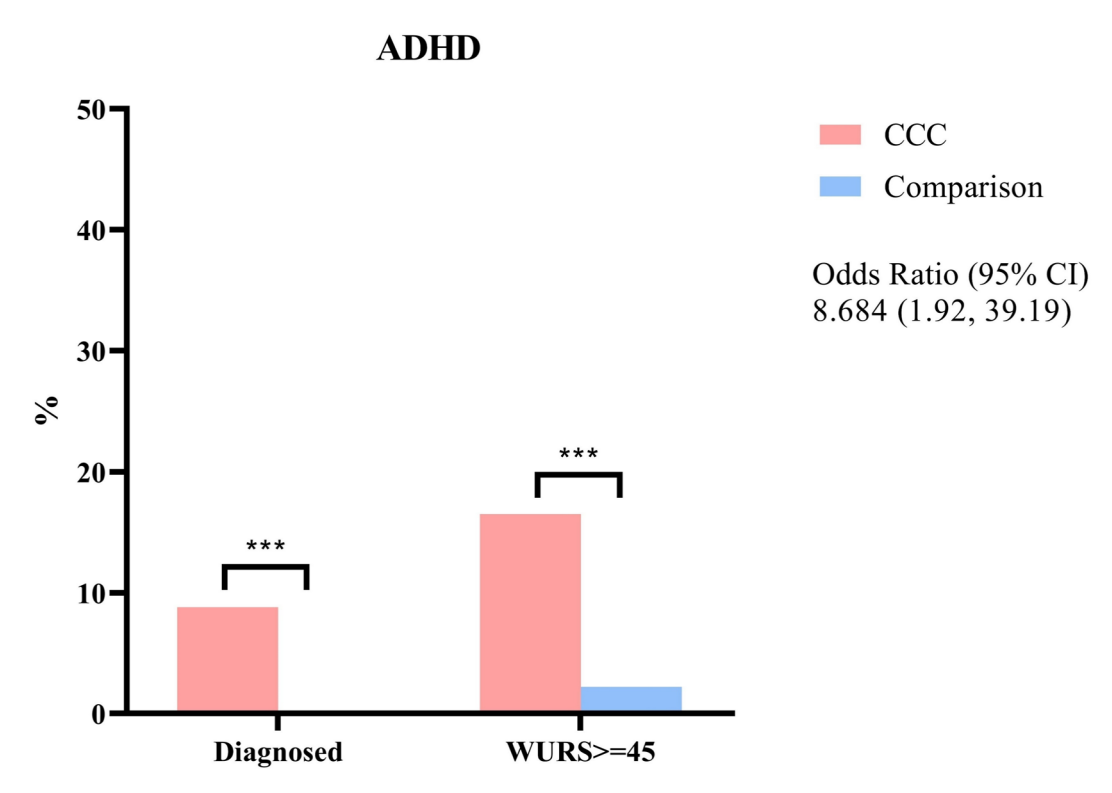
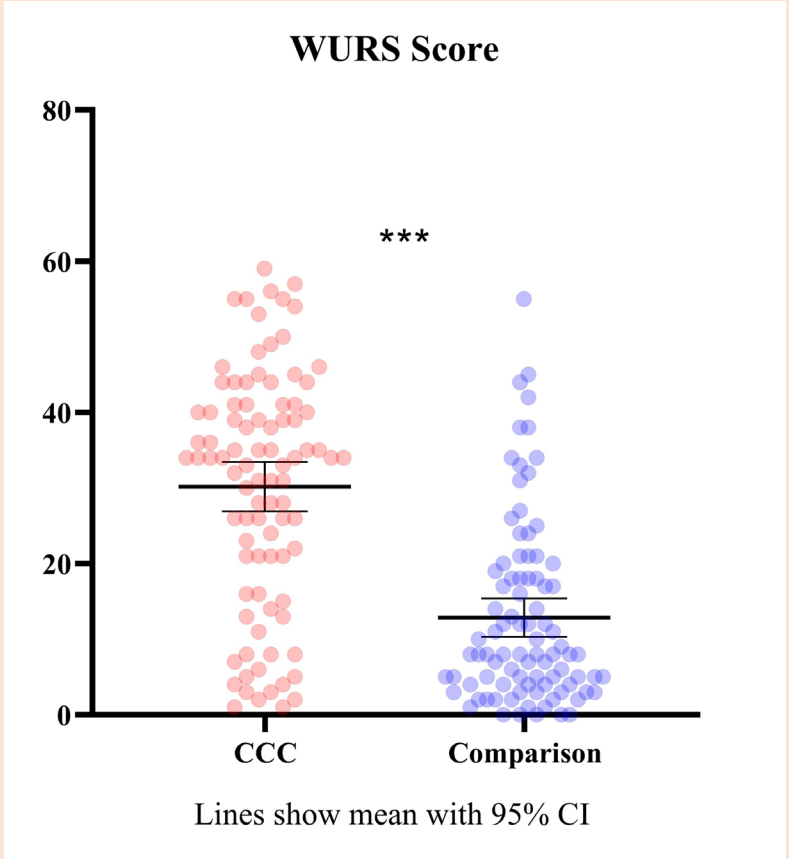
Prevalence of likely ADHD





Quadt…Eccles; in prep

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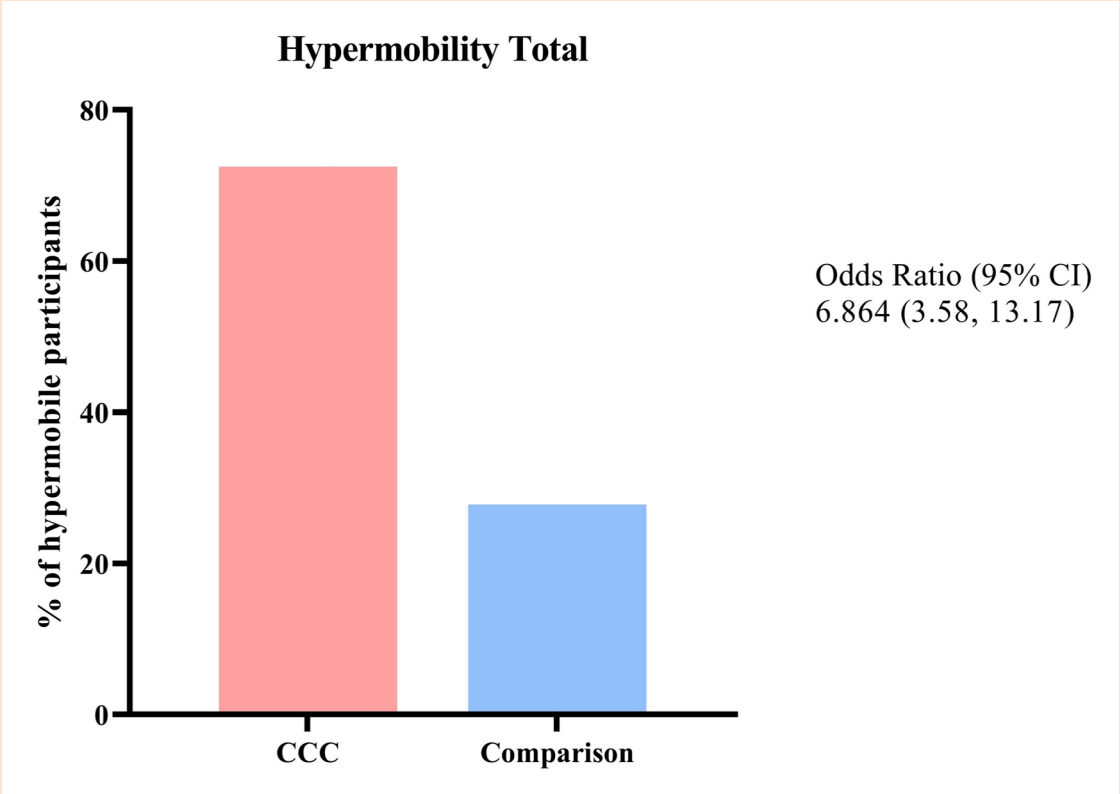
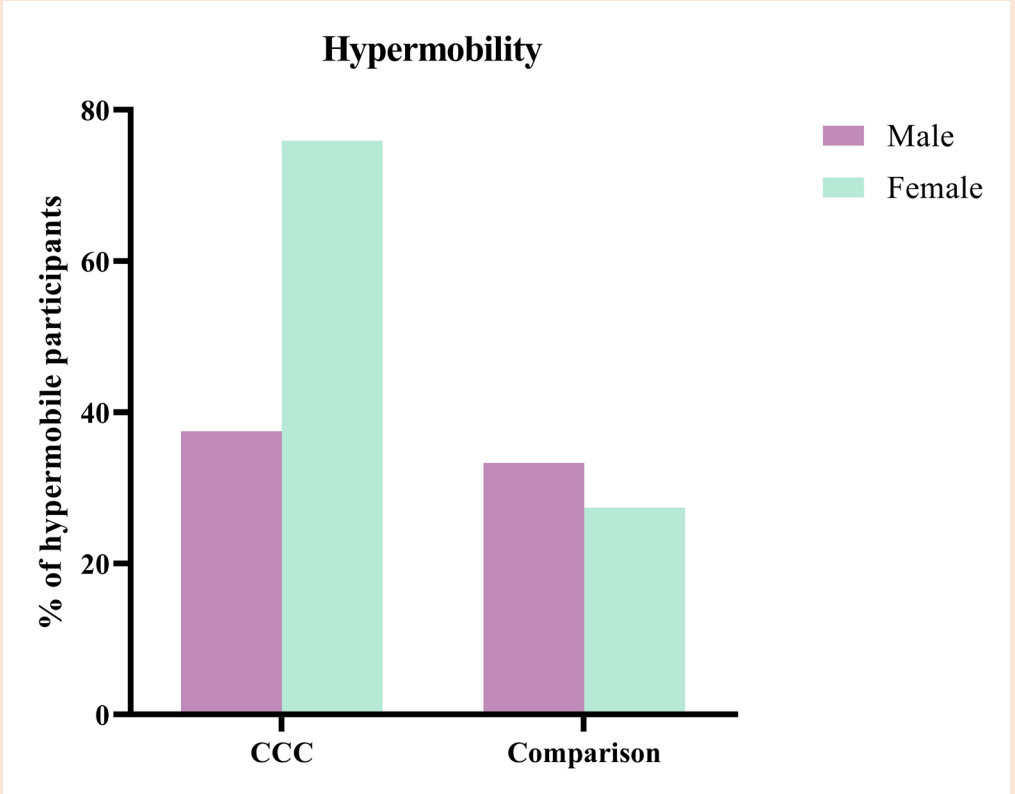
Presence of likely Joint hypermobility





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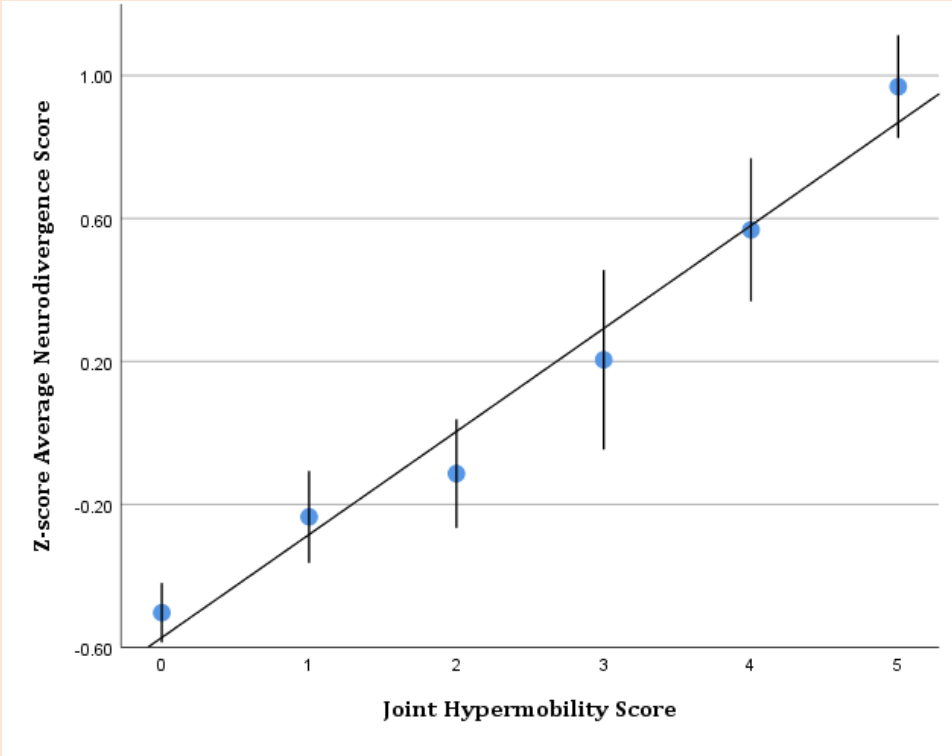

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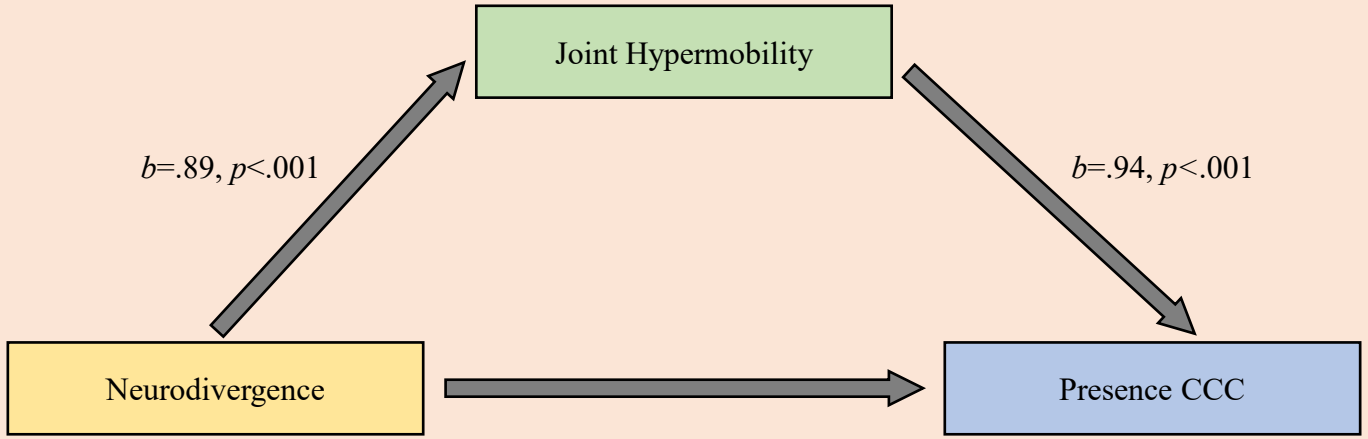
@bendybrain

Mediation Analysis



Direct effect, b=1.31, p<.001
Indirect effect, b=1.68, 95% CI [1.29, 2.42]

Quadt…Eccles; in prep

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nature reviews microbiology

https://doi.org/10.1038/s41579-022-00846-2

Review article

Check for updates

Long COVID: major findings, mechanisms and recommendations

Hannah E. Davis[1], Lisa McCorkell[2], Julia Moore Vogel[3] & Eric J. Topol[3]

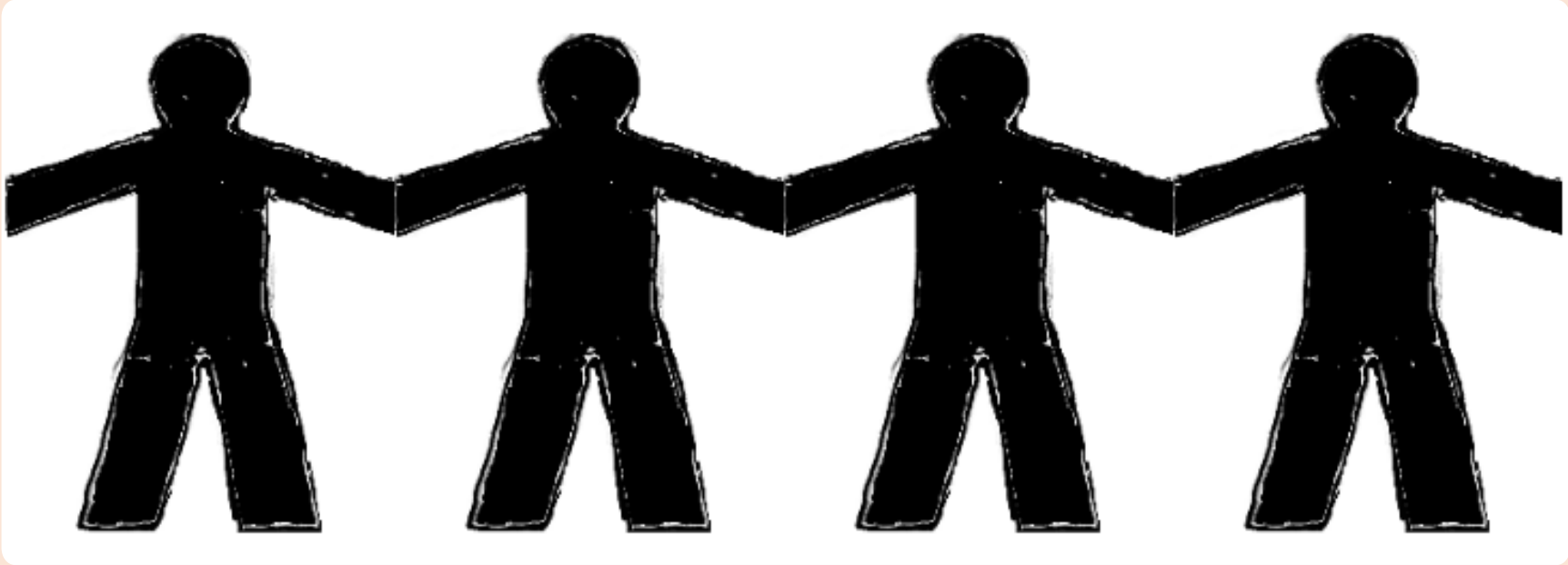
Abstract

Long COVID is an often debilitating illness that occurs in at least 10% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. More than 200 symptoms have been identified with impacts on multiple organ systems. At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily. Biomedical research has made substantial progress in identifying various pathophysiological changes and risk factors and in characterizing the illness; further, similarities with other viral-onset illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome have laid the groundwork for research in the field. In this Review, we explore the current literature and highlight key findings, the overlap with other conditions, the variable onset of symptoms, long COVID in children and the impact of vaccinations. Although these key findings are critical to understanding long COVID, current diagnostic and treatment options are insufficient, and clinical trials must be prioritized that address leading hypotheses. Additionally, to strengthen long COVID research, future studies must account for biases and SARS-CoV-2 testing issues, build on viral-onset research, be inclusive of marginalized populations and meaningfully engage patients throughout the research process.

Sections

Aim

- This study seeks to explore whether generalised joint hypermobility (a marker of variant connective tissue) is a risk factor for self- reported non-recovery from COVID-19 infection.



Why is important to think body-brain

- Nearly half of neurodivergent individuals surveyed by Embracing Complexity (a coalition of neurodevelopmental charities) felt that treatment of mental or physical health symptoms was worse because they were neurodivergent.

- Previous Patient and Public Involvement work conducted by the team tells us that neurodivergent individuals and their families:
  - (1) struggle for years to get an assessment and diagnosis for both mental and physical health problems
  - (2) feel a strong sense of being dismissed, misbelieved or overlooked when interacting with professionals and institutions
  - (3) repeatedly encounter poor understanding and few/no adjustments for their needs within healthcare and educational settings

- Conventional emotion or medication based treatments do not work for all
- This may open up opportunities for novel avenues for personalized body-based treatments for common mental health problems

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Clinician-associated traumatization from difficult medical encounters: Results from a qualitative interview study on the Ehlers-Danlos Syndromes

Colin M.E. Halverson [a b c d], Heather L. Penwell [a], Clair A. Francomano [e]

https://doi.org/10.1016/j.ssmqr.2023.100237

Abstract

Patients with hypermobile Ehlers Danlos Syndrome often experience psychological distress resulting from the perceived hostility and disinterest of their clinicians. We conducted 26 in-depth interviews with patients to understand the origins of this trauma and how it could be addressed in practice. We found that the cumulative effects of numerous negative encounters lead patients to lose trust in their healthcare providers and the healthcare system, and to develop acute anxiety about returning to clinic to seek further care. We describe this as *clinician-associated traumatization*. Ultimately, our interviewees described the result of this traumatization as worse – but preventable – health outcomes.

Exciting projects going on at moment

- Neural correlates of Brain Fog

Amy Kartar

Joel Patchitt

- FLOAT-REST

Dr James Todd

- Brain fog in pregnancy and menopause

Beverly Darkin

slido

What have you learnt today?

ⓘ Start presenting to display the poll results on this slide.

slido

Do you think this will change how you think about your autism work?

ⓘ Start presenting to display the poll results on this slide.

Questions

Thanks

- The funders
- All of the participants and research staff
- Sussex ME/CFS Society and ReMEmber
- CISC @ Brighton and Sussex Medical School
- CIRU @BSUH
- Beth Thompson, Dr Charlie Thompson
- Dr Lisa Quadt, Dr Jenny Csecs, Dr Geoff Davies, Georgia Savage
- Marisa Amato, Dr Kristy Themelis , Dr Ben Towler
- Prof Hugo Critchley
- Prof Kevin Davies
- Prof Neil Harrison
- Prof Sarah Newbury

Find out more

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Linktr.ee/bendybrain

Please check out EDS UK GP toolkit and school toolkit