



The neurobiology of stress: Vulnerability, resilience, and major depression

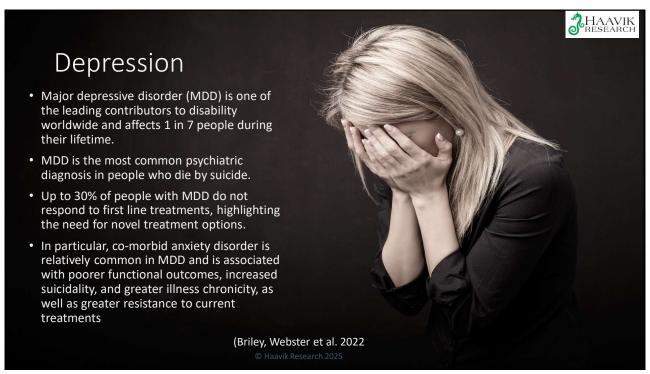
"The Second Pandemic

Over the past few years, the perceived level of psychological stress has risen dramatically across the globe due to a combination of events including the long-lasting Covid-19 pandemic, civil unrest, escalation of political instability across the globe, and climate change that has triggered major environmental and economic perturbations. The consequences of this broad-scale increase in stress are only beginning to be appreciated, but evidence suggests that we are facing a second pandemic of mood and anxiety disorders, including major depression, anxiety, and posttraumatic stress disorder (PTSD)."

(Akil and Nestler 2023)

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(Javaid, Hashim et al. 2023)

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Anxiety

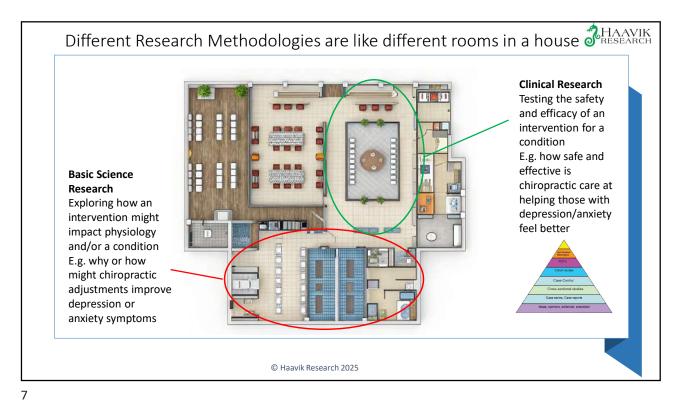
- Anxiety disorders comprise some of the most common mental health conditions
- An estimated 4.05% of the global population has an anxiety disorder
- The number of persons affected has increased by more than 55% from 1990 to 2019.
- Portugal has the highest prevalence (8,671 cases per 100,000), followed by Brazil, Iran, and New Zealand.
- Women are 1.66 times more likely to be affected by anxiety disorders than men.

Outline

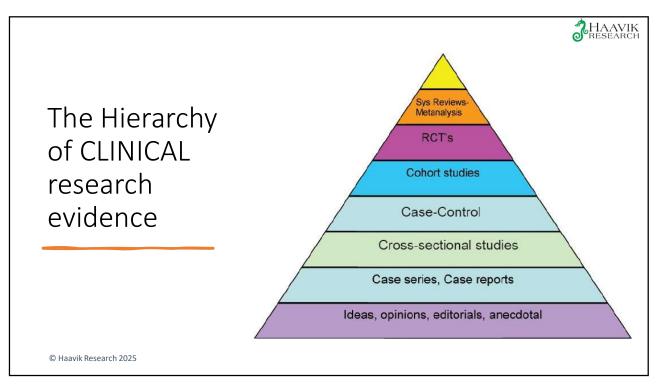
- Clinical research about chiropractic care for people with depression and/or anxiety
 - i.e. studies that can help us know if chiropractic care helps people who suffer with anxiety or depression to feel better
- Basic science research about chiropractic care for people with depression and/or anxiety
 - i.e. how might chiropractic care actually be able to help someone with anxiety or depression?

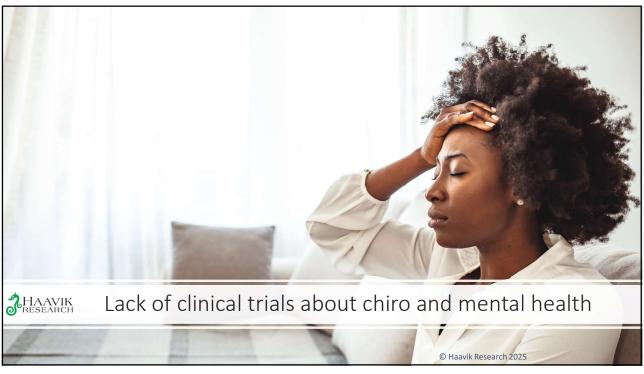
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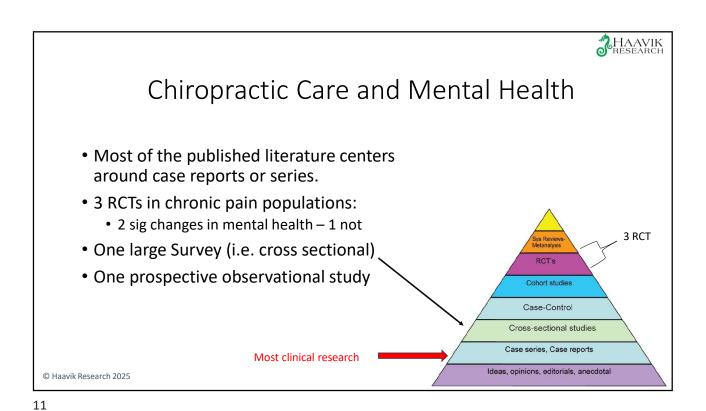
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ChirosAcademy **Research Methods** LEVEL 1 gained any in-depth knowledge about anatomy, physiology, or pathology. Learn the facts about why good spinal function is so important, what happe when we adjust the spine, the detrimental impacts of stress and trauma, the important role of brain mal-adaptations in chronic pain, and how chiropractic care can improve strength and alter the prefrontal cortex and cerebellum RM1.08 How to do a Literature Search RM1.05 Introduction RM1.06 Patient RM1.07 Introduction to Different Researc... Reported Outcome... to Experimental... This class is ideal if you need to design a study yourself if you ha Dr Heidi Haavik Dr. Invan Arriad







4 week Randomised
Controlled Trial

Baseline-Pre-measures

Randomised

CC - Usual Care (N=32)

Post Day-1 measure

Post Day-1 measure

After 4 Weeks Post-Intervention

After 4 Weeks Post-Intervention



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Dr Samran Navid, PhD NZCC

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NEW ZEALAND COLLEGE OF CHIROPRACTIC

Questionnaire Results

Control Group

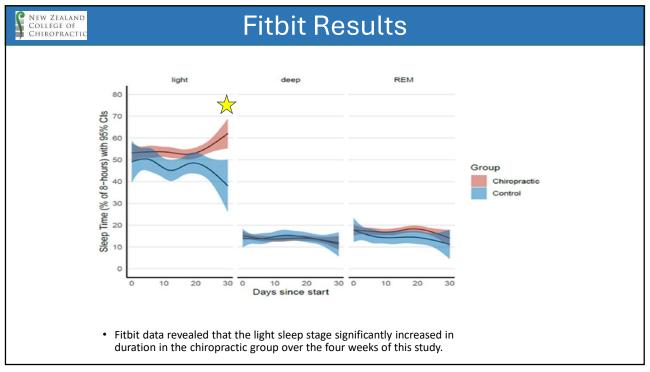
NO significant changes at all

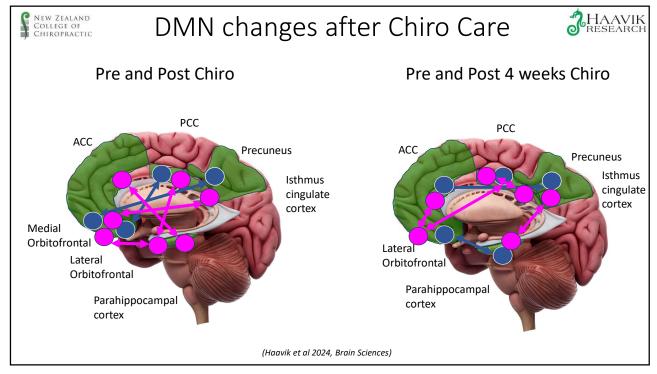
Chiropractic Group

- Improved QOL overall
- Improved Physical function
- Less Depression
- Less anxiety
- Less Fatigue
- Less pain interference
- Less pain intensity











Health-related quality of life among United States service members with low back pain receiving usual care plus chiropractic care vs usual care alone: Secondary outcomes of a pragmatic clinical trial



- All aspects of HRQOL measured in this study (including physical function, pain interference, sleep disturbance, anxiety, depression, and satisfaction with social role) were significantly improved with chiropractic care compared to usual care only.
- The largest effects were for pain (pain interference, worst pain intensity in the past 24hours, pain composite, and pain intensity item).
- While the positive effects found with mental health measures (in chiro group) were statistically significant, the differences between groups were small and below the minimally important difference estimated for similar PROMIS measures
 - (e.g., at 12weeks post-baseline depression and anxiety scale scores differed by about 1T-score point)

(Hays, Shannon, Long, Spritzer, Vining, Coulter, Pohlman, Walter, Goertz, 2022)

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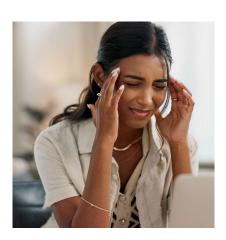
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Efficacy of manual therapy on anxiety and depression in patients with tension-type headache. A RCT



- This study tested whether different kinds of manual therapy could help reduce anxiety and depression in patients with tension-type headaches (TTH)
- 84 people with tension-type headaches; 4 groups; soft tissue technique, articulatory technique, both soft tissue and articulatory technique and control
- Treatments over 4 weeks → assessed right after treatment and again 1 month later.
- Looked at changes in anxiety (trait and state) and depression *Results:* All treatments resulted in a 'moderate' reduction of psychological symptoms associated with TTH

Conclusion: Treatments including an articulatory technique showed a greater efficacy than a soft tissue technique, or a combination of both, for the reduction of TTH-related anxiety and depression levels in these participants.



(Espí-López, López-Bueno et al. 2016)

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Efficacy of manual therapy on anxiety and depression in patients with tension-type headache. A RCT

- "The *suboccipital technique* (ST) aims to relieve affected sub-occipital muscle dysfunction associated with tension-type headaches as these structures may contribute to mobility dysfunction of the occiput-atlas-axis joint"
- "The articulatory technique (AT) was administered to correct and restore the mobility of joints between occiput, atlas and axis. This technique was conducted in the same position as the ST technique (supine position), bilaterally and in two phases that lasted 5 min in all. First, a gentle cephalic decompression as described by Espi´-Lo´pez et al.23 was applied, followed by small circumduction searching for the joint barrier in rotation through selective tension. Second, a high-velocity thrust manipulation in occiput-atlasaxis (OAA) was conducted, performing a cranially directed rotation towards the same side as the circumduction and around a vertical axis passing through the axis, without cervical flexion or extension and minimal side-bending"

(Espí-López, López-Bueno et al. 2016)

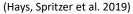
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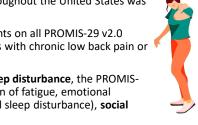
Group and Individual-level Change on Health-related Quality of Life in Chiropractic Patients with Chronic Low Back or Neck Pain

- Prospective observational study: To evaluate group-level and individual-level change in health-related quality of life among persons with chronic low back pain or neck pain receiving chiropractic care in the United States
- A 3-month longitudinal study of 2,024 patients with chronic low back pain or neck pain receiving care from 125 chiropractic clinics at 6 locations throughout the United States was conducted
- Chiropractic care was associated with significant improvements on all PROMIS-29 v2.0
 measures except emotional distress in this sample of patients with chronic low back pain or
 neck pain.
- The largest mean improvements were observed for pain, sleep disturbance, the PROMIS-29 v2.0 mental health summary score (weighted combination of fatigue, emotional distress, ability to participant in social roles and activities and sleep disturbance), social health, and fatigue.
- These improvements over 3 months are consistent with prior estimates of minimally important group-level differences of about 2–3 points for PROMIS measures



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The Prevalence, Patterns, and Predictors of

Chiropractic Use Among US Adults

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Chiropractic,

 Cross-sectional data from the 2012 National Health Interview Survey (n¼34,525) were analyzed to examine the lifetime and 12-month prevalence and utilization patterns of chiropractic use, profile of chiropractic users, and health-related predictors of chiropractic consultations

Changes Owing	to Chiropractic
and Disclosure t	o Personal Health
Care Provider	
Did chiropractic lead to	
Give a sense of control over health	32.5 (30.7-34.3)
Help to reduce stress level or to relax	40.2 (38.4-42.1)
Help to sleep better	41.9 (40.0-43.8)
Helps to feel better emotionally	27.4 (25.7-29.1)
Make it easier to cope with health problems	38.5 (36.6-40.4)
Improve overall health and make you feel better	66.9 (65.1-68.7)
Improve your relationships with others	13.3 (12.0-14.6)
Improve attendance at job or school	17.0 (15.4-18.6)
How important was chiropractic for maintaining	health and well-being
Very important	47.9 (45.9-49.8)
Somewhat important	29.6 (27.8-31.3)
Slightly important	13.9 (12.6-15.2)
Not at all important	8.7 (7.6-9.8)
Used chiropractic for a specific health problem (top health problem)	66.9 (65.1-68.7)

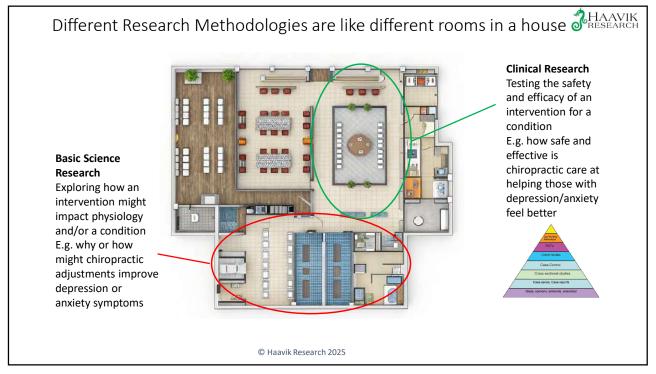
TABLE 2. Reasons for

Using

(Adams, Peng et al. 2017)

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So according to the BRAIN model How might chiropractic care alter mental health?

 Because chiropractic adjustments (of vertebral subluxations) alters brain regions that are essential for feeling good, for emotional resilience and good mental health



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The Brain, Anxiety and Depression

- Key factors to consider regarding the mechanisms of depression and anxiety are (Bisgaard, Allin et al. 2022):
 - Pro-inflammatory cytokines (consider Gut dysbiosis, diet)
 - Vagal nerve signaling (PSN)
 - · Genetics
 - Changes in brain signaling and morphology



- Many neurobiological and neuroendocrinological studies have reported alterations in prefrontal-limbic pathways (including amygdala and hippocampus), serotonergic projections and the hypothalamic-pituitary-adrenal (HPA) axis (Chen 2022; Ghasemi, Navidhamidi et al. 2022)
- Studies have also found Depression and Anxiety are linked with plastic changes in the **Default Mode** Network (Briley, Webster et al. 2022; Menon, 2011)

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Triple Brain Network and Psychopathology

The science of large-scale brain networks offers a powerful paradigm for investigating cognitive and affective dysfunction in psychiatric and neurological disorders. This review examines recent conceptual and methodological developments which are contributing to a paradigm shift in the study of psychopathology. I summarize methods for characterizing aberrant brain networks and demonstrate how network analysis provides novel insights into dysfunctional brain architecture. Deficits in access, engagement and disengagement of largescale neurocognitive networks are shown to play a prominent role in several disorders including schizophrenia, depression, anxiety, dementia and autism. Synthesizing recent research, I propose a triple network model of aberrant saliency mapping and cognitive dysfunction in psychopathology, emphasizing the surprising parallels that are beginning to emerge across psychiatric and neurological disorders.

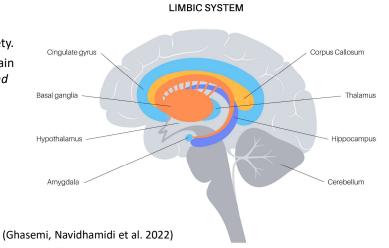
(Menon 2011)

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"Anxiety and hippocampal neuronal activity: Relationship and potential mechanisms."

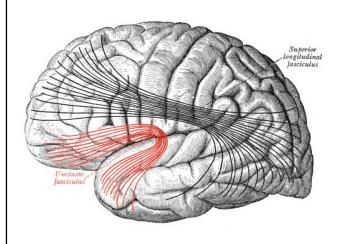
- "The hippocampus has been implicated in modulating anxiety.
- It interacts with a variety of brain regions, regulating emotion and stress responses and adjusting anxiety levels in response to a variety of stressful conditions
 - prefrontal cortex
 - amygdala
 - · hypothalamus
 - nucleus accumbens



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A meta-analysis on the uncinate fasciculus in depression

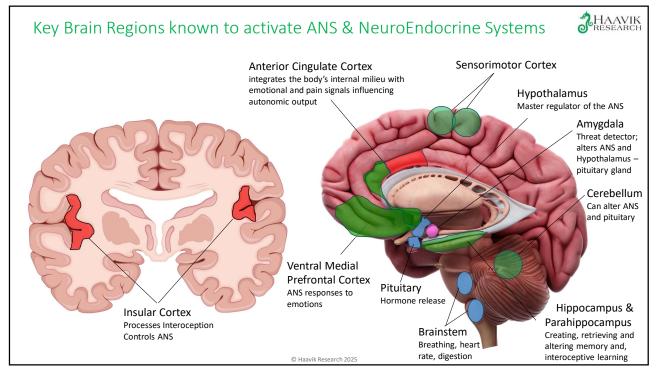




- Aberrant microstructure of the uncinate fasciculus, a white matter tract implicated in emotion regulation, has been hypothesized as a neurobiological mechanism of depression.
- The uncinate fasciculus is a white matter tract in the brain (essentially a bundle of myelinated axons) that connects:
 - the anterior temporal lobe (including areas important for memory and emotion like the anterior parahippocampus and amygdala) with the
 - orbitofrontal cortex (part of the frontal lobe involved in decision-making, social behavior, and emotional regulation).

(Xu, Nguyen et al. 2023)

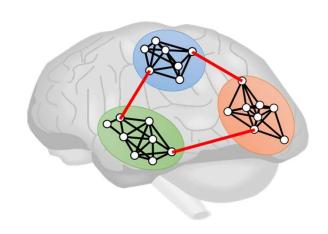
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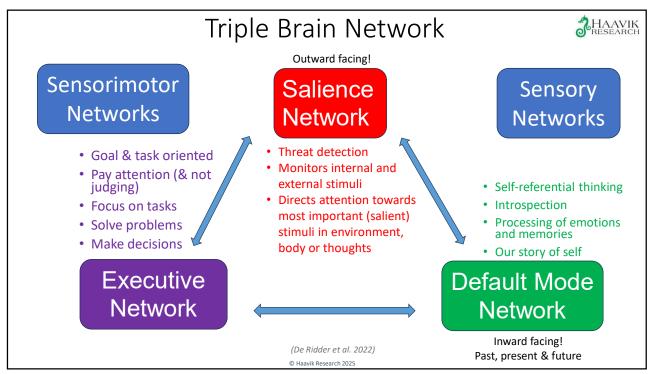
Biological Networks in the Brain (and Hubs)

- A biological neural network in the brain is a complex network of neurons that are chemically connected by synapses.
- Neurons send and receive electrochemical signals to each other, and the brain uses these signals to process information.



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Functional connectivity in people with both Anxiety & Depression

- "This systematic review examined differences in resting-state brain connectivity associated with anxiety comorbidity in young- and middleaged adults with MDD, with the aim of identifying novel targets for neuromodulation treatments, as these treatments are thought to work partly by altering dysfunctional connectivity pathways."
- "Only two studies included people with MDD and formally diagnosed comorbid anxiety disorders; the remainder included people with MDD with dimensional anxiety measurement."
- "There was evidence for dysconnectivity between the amygdala and other brain networks in depression with co-morbid anxiety, and an indication that abnormalities of default mode network connectivity may play an underappreciated role in this condition."

(Briley, Webster et al. 2022)

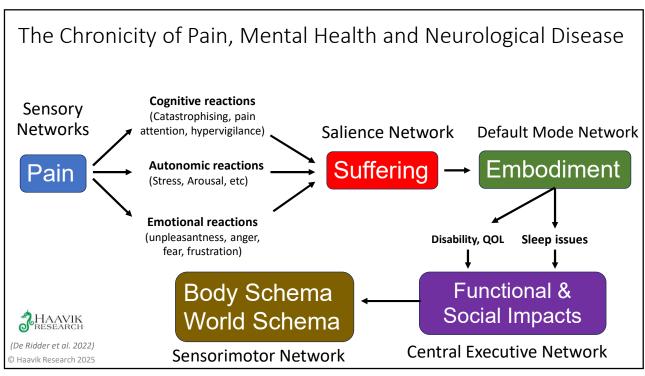
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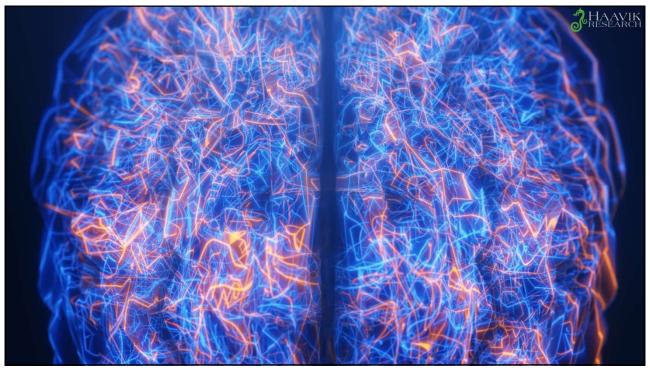
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Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: a transdiagnostic multimodal meta-analysis of structural and functional MRI studies

- "Major depressive disorder (MDD), anxiety disorders (ANX), and chronic pain (CP) are frequent disorders of brain and behavior"
- "High comorbidity and overlapping risk factors, such as chronic and/or acute life stress, suggest overlapping neural correlates, i.e., similar changes in large-scale brain systems mediating between microscopic alterations and behavioral dysfunctions".
- "Indeed, shared structural [8–10] and functional [11–14] changes in prefrontal-insular circuits, for example, have been reported in all three disorders."
- "Using coordinate-based meta-analysis, we provide first-time evidence for common and specific large-scale brain changes in major depression, anxiety disorders, and chronic pain."
- "Common changes concerned gray matter volume loss in insular and prefrontal cortices
 of default-mode and salience networks, suggesting a neural correlate for comorbidity
 and possibly shared chronification mechanisms."

(Brandl, Weise et al. 2022)





Bidirectional comorbid associations between back pain and major depression in US adults



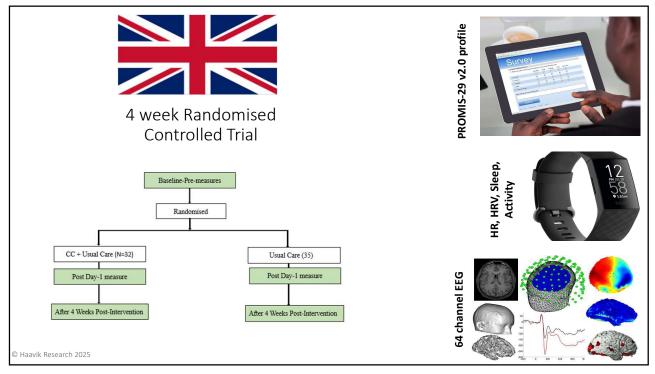
- Low back pain and depression have been globally recognized as key public health problems and they are considered co-morbid conditions.
- The cross-sectional analysis showed significant associations between back pain and major depression.
- The longitudinal analysis indicated that back pain at baseline was prospectively associated with major depression at follow-up, controlling for health behavioral and demographic variables.
- Major depression at baseline was also prospectively associated with back pain at follow-up, controlling for a set of related confounders.
- These findings of a bidirectional comorbid association fill a gap in the current understanding of these comorbid conditions and could have clinical implications for the management and prevention of both depression and low back pain.

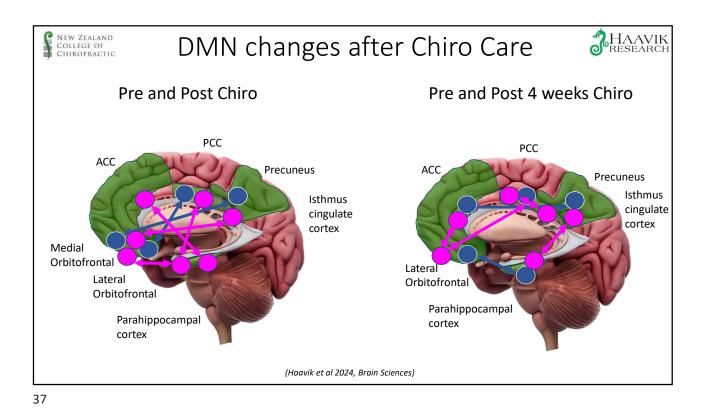
(Yang, Hurwitz, Li, de Luca, Tavares, Green & Haldeman 2023)



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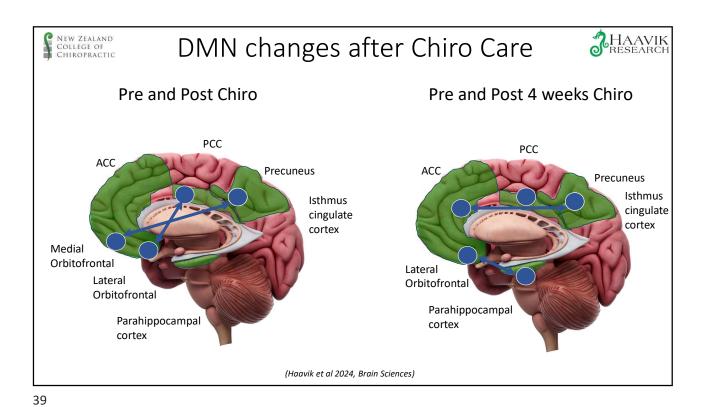
Unmedicated depressed people have significantly increased functional connectivity between the Precuneus and the prefrontal cortex

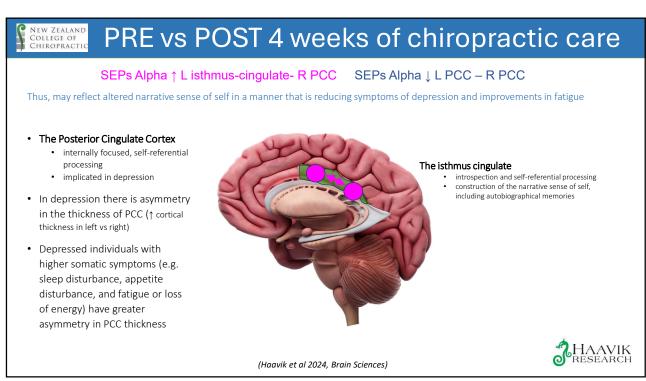
Increased functional connectivity of the posterior cingulate cortex with the lateral orbitofrontal cortex in depression (Cheng, Rolls et al. 2018B)

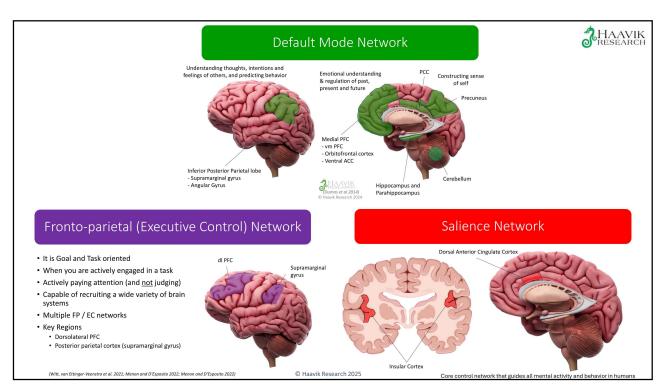


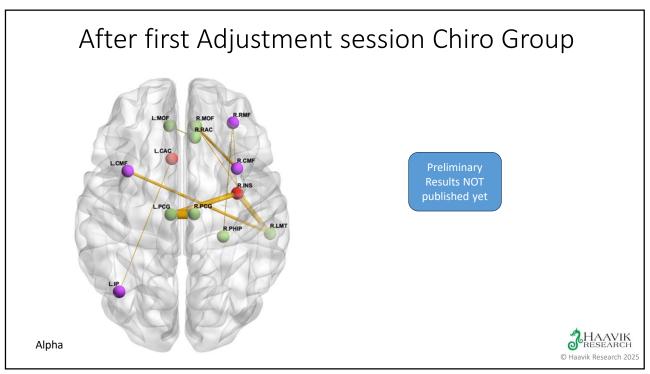
The increased connectivity of the precuneus and/or PCC with the prefrontal cortex short-term memory system may contribute to the rumination about low self-esteem in depression.

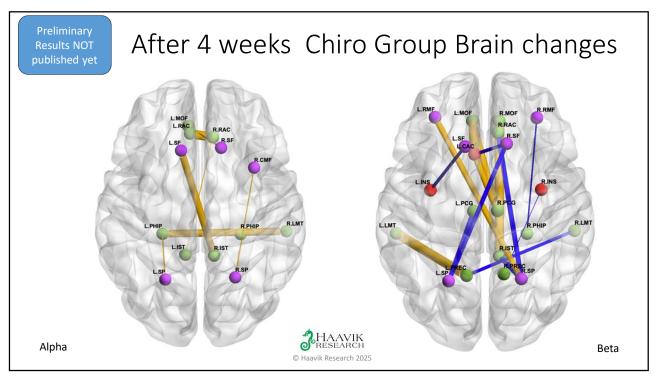
(Cheng, et al 2018A; Cheng, Rolls et al. 2018B)

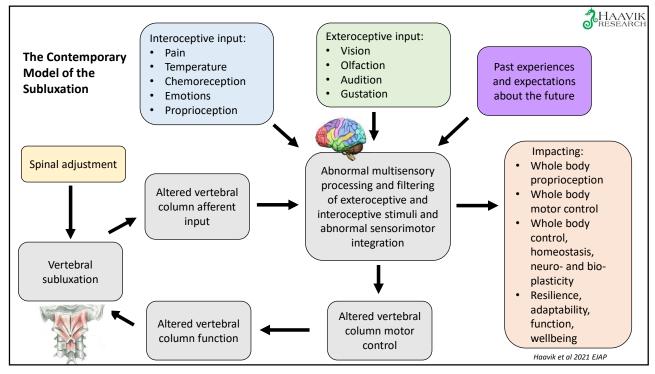


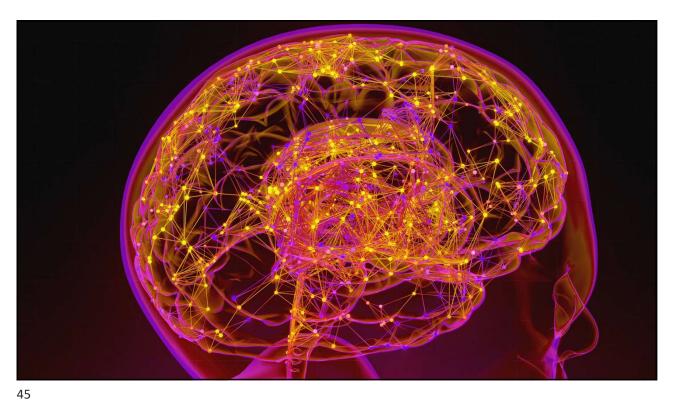




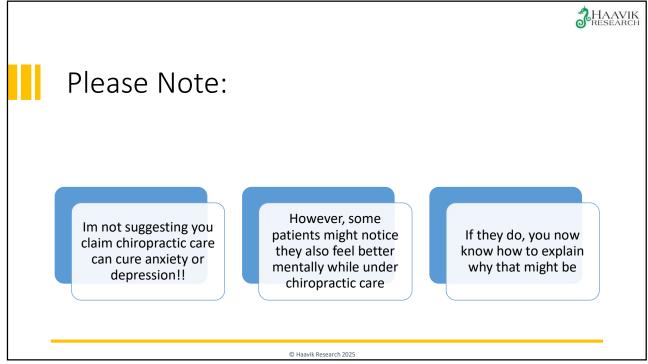








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Effect of breathwork on stress and mental health: A meta-analysis of randomised-controlled trials

- · Deliberate control of the breath (breathwork) has recently received an unprecedented surge in public interest and breathing techniques have therapeutic potential to improve mental health.
- Across all studies combined, the intervention produced a moderate, statistically significant reduction in both anxiety and depression symptoms as reported by participants themselves

(Fincham, Strauss et al. 2023)

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At least 1 non-muskuloskeletal improvement

was reported after the previous chiropractic

session in 21% to 25% of cases.

Of these responses, 26% (highest response) were related to the airway passages (usually reported as "easier to breathe"), 25% were related to the digestive system (mostly reported as "improved function")

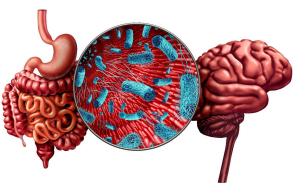
(Leboeuf-Yde, Axén et al. 1999)

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"The gut microbiome exerts a considerable influence on human neurophysiology and mental health. Interactions between intestinal microbiology and host regulatory systems have now been implicated both in the development of psychiatric conditions and in the efficacy of many common therapies. With the growing acceptance of the role played by the gut microbiome in mental health outcomes, the focus of research is now beginning to shift from identifying relationships between intestinal microbiology and pathophysiology, and towards using this newfound insight to improve clinical outcomes. Here, we review recent advances in our understanding of gut microbiome-brain interactions, the mechanistic underpinnings of these relationships, and the ongoing challenge of distinguishing association and causation. We set out an overarching model of the evolution of microbiome-CNS interaction and examine how a growing knowledge of these complex systems can be used to determine disease susceptibility and reduce risk in a targeted manner."



The gut microbiome and mental health: advances in research and emerging priorities



(Shoubridge, Choo et al. 2022) © Haavik Research 2025



- Briley, P. M., et al. (2022). "Resting-state functional connectivity correlates of anxiety co-morbidity in major depressive disorder." Neuroscience & Biobehavioral Reviews 138: 104701.
- Xu, E. P., et al. (2023). "A meta-analysis on the uncinate fasciculus in depression." <u>Psychological Medicine</u> **53**(7): 2721-2731.
- Ghasemi, M., et al. (2022). "Anxiety and hippocampal neuronal activity: Relationship and potential mechanisms." Cognitive, Affective, & Behavioral Neuroscience 22(3): 431-449.
- Yang, H., et al. (2023). "Bidirectional comorbid associations between back pain and major depression in US adults." International Journal of Environmental Research and Public Health 20(5): 4217.
- De Ridder, D., et al. (2022). "Pain and the triple network model." Frontiers in neurology 13: 757241.
- Menon, V. (2011). "Large-scale brain networks and psychopathology: a unifying triple network model." <u>Trends in Cognitive Sciences</u> 15(10): 483-506.
- Haavik, H., et al. (2024). "Neuroplastic Responses to Chiropractic Care: Broad Impacts on Pain, Mood, Sleep, and Quality of Life." Brain Sciences 14(11): 1124.
- Hays, R. D., et al. (2019). "Group and individual-level change on health-related quality of life in chiropractic patients with chronic low back or neck pain." Spine 44(9): 647-651.
- Hays, R. D., et al. (2022). "Health-related quality of life among United States service members with low back pain receiving usual care plus chiropractic care vs usual care alone: Secondary outcomes of a pragmatic clinical trial." Pain Medicine 23(9): 1550-1559.
- Espí-López, G. V., et al. (2016). "Efficacy of manual therapy on anxiety and depression in patients with tension-type headache. A randomized controlled clinical trial." International Journal of Osteopathic Medicine 22: 11-20.
- Adams, J., et al. (2017). "The prevalence, patterns, and predictors of chiropractic use among US adults: Results from the 2012 National Health Interview Survey." Spine 42(23): 1810-1816.
- Yang, H., et al. (2023). "Bidirectional comorbid associations between back pain and major depression in US adults." <u>International Journal of Environmental Research</u> and Public Health 20(5): 4217.
- Akil, H. and E. J. Nestler (2023). The neurobiology of stress: Vulnerability, resilience, and major depression, National Academy of Sciences. 120: e2312662120.
- Chen, C. (2022). "Recent advances in the study of the comorbidity of depressive and anxiety disorders." <u>Advances in Clinical and Experimental Medicine</u> 31(4): 355-358.
- Bisgaard, T. H., et al. (2022). "Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment." <u>Nature reviews Gastroenterology</u> & hepatology 19(11): 717-726.
- Cheng, W., Rolls, E.T., Qiu, J., Yang, D., Ruan, H., Wei, D., Zhao, L., Meng, J., Xie, P. and Feng, J., 2018. Functional connectivity of the precuneus in unmedicated
 patients with depression. <u>Biological Psychiatry: Cognitive Neuroscience and Neuroimaging</u>, 3(12), pp. 1040-1049.
- Javaid, S. F., et al. (2023). "Epidemiology of anxiety disorders: global burden and sociodemographic associations." Middle East Current Psychiatry 30(1): 44.
- Shorey, S., et al. (2022). "Global prevalence of depression and elevated depressive symptoms among adolescents: A systematic review and meta-analysis." British
 journal of clinical psychology 61(2): 287-305.

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Questions?

