WINTER 2023

FORCE NET
FORCE-BASED MECHANISMS

NEWSLETTER

WHAT CAN ANIMAL RESEARCH TELL US ABOUT MECHANISMS OF MANUAL THERAPY?

Bill Reed, DC, PhD

Manual therapy has been used for thousands of years to convey purported health benefits for a wide variety of health conditions. Unfortunately, manual therapy clinical outcomes often demonstrate only mild to moderate improvements as the sub-populations most likely to benefit from various types of manual therapy have yet to be identified. This impediment to clinical optimization and appropriate utilization of manual therapy is thought to be due to our lack of understanding of the underlying mechanisms of manual therapy (or basically, not understanding how manual therapy actually works).

The involved mechanisms are most likely complex and multi-faceted, thereby emphasizing the present need of more mechanistic-oriented in vivo manual therapy research in humans and animals. Animal studies are often conducted with the intent to provide greater understanding with regard to biological effects and/or dose-response relationships of a particular therapeutic intervention (including manual therapy). For example, our laboratory has been using a rodent model of muscular low back pain induced by a neurotrophin (nerve growth factor-NGF) to investigate the effect of spinal mobilization on pain-related neuropeptides (such as calcitonin gene-related neuropeptide-CGRP) (1). We recently reported that 10 minutes of daily passive mechanically-delivered spinal mobilization (starting at Day 0) in adult rats prevented the development of NGF-induced low back pain. While injection of NGF increased the expression of pain-related CGRP in the dorsal root ganglion (location of peripheral sensory neuron cell bodies), spinal mobilization effectively negated this increase in CGRP expression.

However, in subsequent experiments in which we allowed the NGF-induced low back pain to fully develop prior to beginning daily spinal mobilization treatments at Day 10, mechanical low back pain was not reduced (unpublished data). Our preventative but not delayed treatment findings with spinal mobilization mirrored similar findings with massage therapy using a rat model of repetitive-strain injury (2, 3). Another rodent study using a third animal pain model complete Freund adjuvant) demonstrated that ankle joint (mobilization reduces nociceptive behavior and pro-inflammatory cytokines IL-β and TNF in spinal cord tissues (4).

This pain study demonstrated both central and peripheral neuroimmuno-modulatory effects following manually applied peripheral joint mobilization. These examples of recent animal studies involving mechanically or manually applied joint mobilization or massage therapy are important early steps in beginning to tease out and identify the mechanisms responsible for the decreased pain/nociception and other clinical benefits attributed to manual therapy treatment. Future mechanistic-oriented animal studies can be used to help identify which clinical sub populations would most likely benefit from manual therapy treatment and when best to begin and/or end manual therapy interventions.

CITATIONS

1. Reed WR et al. Front Neurosci 2020,14:385. PMID: 32425750.
2. Barbe MF et al. BMC Musculoskel Disord 2021, 22:417. PMID 33952219.
3. Barbe MF et al. Front Physiol 2021, 12:755923. PMID: 34803739.
4. Omura CM et al. Front Physiol 2022, 14:816624. PMID: 35095573.

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KICKOFF Recap

MECHANISMS: CRITICAL YET (STILL) UNDERSTUDIED COMPONENTS OF TREATMENT DEVELOPMENT, TESTING, AND IMPLEMENTATION

THE FOLLOWING ARE KEY HIGHLIGHTS FROM DR. BURNS' KEYNOTE ADDRESS

- What we *really* want to know is if manual therapy treatment actually causes the clinical outcomes - and if so, how it works remains a critical and compelling question.
- Despite vast differences in delivery/methodology, many Force-Based Manipulations (FBM) and other non-pharmacological approaches are generally modest with no evidence of superiority. This suggests that these vastly different non-pharmacological treatment approaches might share common attributes. To discover these mechanisms, we need to look at more than just pre-post treatment changes.

Kickoff Keynote Speaker, Dr. John Burns, Rush University Medical Center

For those who were unable to attend the ForceNET Kickoff Event on January 17th, you can watch the entire 1 hour event by going to the ForceNET website at **https://sites.duke.edu/forcenet/**

WITHOUT MECHANISTIC-ORIENTED RESEARCH:

- We cannot tell whether the treatment works for reasons specified by theory or via some other pathway;
- We cannot discriminate effective elements of treatment from redundant or inert elements;
- We do not have the theoretical and empirical principles by which to enhance treatments;
- We cannot specify what exactly must be preserved in treatments as we move from controlled RCTs to clinical practice settings;
- We do not have empirically-supported rationale for asking people in pain to engage in specific types of treatment, as "it seems to work but we are not sure why, is no longer good enough."

RULES OF EVIDENCE THAT NEED TO BE ACCOMPLISHED

1. Design studies to test mechanisms not just outcomes.
2. Compare multiple active treatments.
3. Take frequent assessments (minimally after each session).
4. Include multiple specific and non-specific mechanisms.
5. Use lagged and cross-lagged analysis over session-by-session epochs.
6. Perform analysis to test unique and common effects.
7. Investigate timing and/or rate of changes.

WHAT 5 THINGS DO WE NEED TO KNOW TO SAY THAT A MECHANISM IS SPECIFIC?

1. Substantial change in mechanism predicts later change in outcome.
2. Early change in mechanism predicts later change in outcome (i.e. lagged correlation).
3. Change in mechanism is specific to the unique treatment approach.
4. Mechanism change has some degree of unique relationship with outcome changes beyond effects of non-specific mechanisms.
5. Timing in mechanism change corresponds to application and technique.

GOING FORWARD WE MUST:

1. Identify key mechanisms within kinds (types) of current treatment approaches;
2. Identify key mechanisms across kinds (types) of current treatment approaches;
3. Identify potential mechanisms and refine treatment approaches to active them;
4. Identify matching factors, moderators, and predictors.

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ForceNET Pilot Grants

PILOT AWARDS UP TO $50,000 (INDIRECT INSTITUTIONAL COSTS ARE LIMITED TO 15% OF TOTAL BUDGET REQUESTED)

Two annual submission cycles (LOI due: March/Sept 1st; applications due: June/October 1st)

- Submit applications via ForceNET website: **https://sites.duke.edu/forcenet/**

Must be mechanistic-oriented and involve force-based manipulations (massage, touch, manipulation, mobilization).

MUST INVOLVE 1 OR MORE OF THESE PRIORITY AREAS:

1. Biomechanical metric development
2. Neural mechanosensory transduction (physiological mechanisms)
3. Psychosocial/contextual mechanisms

Primary study outcomes **cannot** be "patient centered outcomes" (often not mechanistic).

Principle Investigators are required to be in the United States, but Co-Investigators can be international (see RFA for details).

Submit pilot application to only **one** force-based manipulations U24 network.

IRB/IACUC approval required & **Project Duration 1 Year.**

3 High-Priority Areas

1. **FBM Biomechanical Metric Development** – to characterize and quantify the types of in vivo superficial or deep mechanical forces associated with FBM application using universally accepted scientific metrics and terminology.
2. **FBM Neural Mechanosensory Transduction (physiological mechanisms)**– to identify multiscale responses that underlie the physiological effects related to Force-Based Manipulations.
3. **FBM Psychosocial/Contextual Mechanisms** – to identify how contextual factors interact with therapeutic forces. Examples of psychosocial/ contextual factors of interest include, but are not limited to: social touch, patient/clinician relationship for delivery of therapeutic forces, etc.

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