THE EFFECTS OF FUNCTIONAL RE-ADAPTIVE EXERCISE DEVICE INTERVENTION FOR LUMBOPELVIC RECONDITIONING IN ASTRONAUTS AND TERRESTRIAL POPULATIONS

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The Effects of Functional Re-Adaptive Exercise Device Intervention for Lumbopelvic Reconditioning in Astronauts and Terrestrial Populations

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Abstract

Lumbopelvic muscle deconditioning after long-duration spaceflight and Chronic Low Back Pain can lead to dysfunction, pain, and lost workdays. Reconditioning Lumbar Multifidus and Transversus Abdominis have so far proved to be challenging. To improve rehabilitation outcomes, a novel exercise device called the Functional Re-adaptive Exercise Device (FRED) was developed to target the lumbopelvic muscles specifically; however, it has only been tested in healthy participants.

This Thesis aimed to test if FRED could be used as a rehabilitation tool in patients with Chronic Non-Specific Low Back pain and a simulated post-flight astronaut population after 60-days of head-down-tilt-bed rest. A holistic mixed-method approach was taken, with primary outcome measures considering patient-reported outcomes for function and pain, Lumbar Multifidus and Transverse Abdominis muscle size using ultrasound and MRI and static and functional balance performance.

This thesis is the first to use FRED in two target populations. In the first study of Chronic Low Back Pain, patients did FRED for three 15 minutes sessions per week for six weeks, with improvements in self-reported function and pain symptoms and increased Lumbar Multifidus cross-sectional area. In the second study, during the Artificial Gravity ESA/ NASA bed rest study, daily FRED exercise for 13 days for up to 30 minutes improved pain perception. It increased the Lumbar Multifidus muscle cross-sectional area. FRED had the greatest improvement of dynamic movement control in participants who did not receive an artificial gravity intervention. There was also intriguing new evidence that FRED might have a role in physical fatigue monitoring. The results show that FRED can be used successfully as a rehabilitative and reconditioning tool in clinical and simulated spaceflight populations.

Table of Contents

Table of Tables

Table of Figures

Tables of Equations

Publications and Conferences

Lindsay, K., Caplan, N., Weber, T., Salomoni, S., De Martino, E., Winnard, A., ... & Debuse, D. (2020). Effects of a six-week exercise intervention on function, pain and lumbar multifidus muscle cross-sectional area in chronic low back pain: A proof-of-concept study. Musculoskeletal Science and Practice.

Lindsay, K., Caplan, N., and Debuse, D. As Below, so Above: Structural changes to the Lumbar Multifidus and Transverse Abdominus muscles after 6 weeks of FRED intervention on Earth and what this might tell us about back pain in Space. Oral Presentation. Northumbria University Health and Life Science PGR Conference, Newcastle. (2017)

Abbreviation list

Abbreviation used	Full text
A1-A5	Assessment 1-A5 (Low Back Pain Study)
ADIM	Abdominal Drawing in Manoeuvre
ADL	The activity of Daily Living
AGBRESA	ESA/ NASA Artificial Gravity 60-dy Head Down Tilt bed rest study
A-P	Anterioposterior
ARED	Advanced Resistive Exercise Device.
BDC	Baseline Data Collection
BEC	Bilateral standing, eyes closed
BEC_foam	Bilateral standing, eyes closed on a foam cushion
BEO	Bilateral standing, eyes open
BEO_foam	Bilateral standing, eyes open on a foam cushion
BMI	Body Mass Index
BW	Bodyweight (normally using pre-flight as a reference)
C1/2/2+	Campaign 1 (summer) 2 (winter) 2+ (additional winter) AGBRESA
CEVIS	Cycle Ergometer with Vibration Isolation System
CoP	Centre of Pressure
CSA	Cross Sectional Area
DLR	Deutsches Zentrum für Luft- und Raumfahrt / Germany Aerospace Centre
EMG	Electromyography
EO	External Obliques
ESA	European Space Agency
FD	Flight-day
HDT	Head-down tilt (day number of BR study in head-down position)
HIIT	High-Intensity Interval Training
iEMG	Intramuscular Electromyography
IO	Internal Obliques
IVD	Intravertebral Disc
L-	Days leading up to spaceflight (L-0 = launch day)
LBP	Low back pain
LM	Lumbar Multifidus
MCID	Minimal Clinically Important Difference
MCS/ PCS	Mental or Physical Component Score (SF-36)
M-L	Mediolateral
MRI	Magnetic Resonance Imaging
NASA	National Aeronautics and Space Administration
NRS	numeric rating scale for pain
PSFS	Patient-Specific Functional Scale
R+	Days following spaceflight (R+0 = re-entry day)
RSA	Roscosmos State Corporation for Space Activities
SABP	Space adaptation back pain
SD	Standard deviation from the mean
TM	Treadmill
TrA	Transverus Abdominis
TVIS	Treadmill with Vibration Isolation System
USI	Ultrasound image/ Imagining
USOS	United States Operating Segment, the front half of the ISS
VAS	Visual Analogue Score

Acknowledgements

Whether you consider it standing on the shoulders of giants or turtles all the way down, a PhD journey is the most intense individual team effort.

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Declaration

I declare that the work contained in this Thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others. This work was supported by funding from the European Space Agency.

Any ethical clearance for the research presented in this Thesis has been approved. Approval has been sought and granted by The Ethics Committee of the Northern Rhine Medical Association (Düsseldorf, Germany, Application No. 2018143). The AGBRESA study was registered in the German Clinical Trial Register (DRKS) under No. DKRS00015677) and LBP study received ethical approval from the Faculty Review Board (reference HLSDD200516, 05/07/2016) and the European Space Agency Medical Board,The study was registered with ClinicalTrials.gov, number NCT03062293.

I declare that the word count of this Thesis is 42,708 words.

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1 Introduction

"We choose to go to the Moon in this decade, and do the other things, not because they are easy but because they are hard" (Kennedy, 1962) is the quote from American President John F. Kennedy on September 12th, 1962 which kick-started human planetary exploration. The human space race had started the year before when Russian cosmonaut, Yuri Gagarin, launched aboard his Vostok capsule on April 12th, 1961 (Jenks, 2012). In the nearly 60 years since Kennedy's infamous words, human spaceflight has visited the Moon, undertaken short duration Low Earth Orbit (LEO) missions on the Space Shuttle, and undertaken extended duration missions on space stations such as Salyut, Skylab and MIR (Space, 2012). Since 2000, humans have inhabited space continuously on the largest space station to date, the International Space Station (ISS) (Dunbar, 2020). The ISS is a multinational LEO laboratory where crews typically spend five months to a year (Uri, 2020). Future human spaceflight missions are even more ambitious, with Gateway, a trans-lunar outpost acting as a staging post for future missions to the Moon and Mars, planned for the near future (Gerstenmaier & Crusan, 2018).

However, human exploration comes with risks that need to be managed and minimised. Exposure to the microgravity environment is deleterious to the function of the human body; the musculoskeletal, cardiovascular and neurovestibular systems adapt to the microgravity environment, leading to deconditioning (Baker & Wear, 2008; Buckey, 2006; Pool-Goudzwaard et al., 2015). These adaptations are relatively harmless in space; however, upon return to Earth, with a normal gravitational acceleration of -9.81ms-2 (or +1Gz), re-adaptation can be painful and place the astronauts at increased risk of injury (Johnston et al., 2010). To reduce this risk, astronauts undertake a varied exercise countermeasure programme while in orbit, training for up to 1.5 hours per day, as well as post-flight reconditioning (Loehr et al., 2015; Petersen et al., 2016). Countermeasures include exercises such as treadmill running, resistance training and cycle ergometry. One area that current in-flight exercise countermeasures have not successfully addressed is paraspinal musculoskeletal deconditioning and associated low back pain (LBP) (Bailey et al., 2018; Chang et al., 2016; Hides et al., 2016; Hides et al., 2021).

Upon their return to Earth, astronauts also undertake a reconditioning program, which has a graded increase in exercise difficultly from pool work to regular gym-based training (Lambrecht et al., 2017; Loehr et al., 2015). Reducing pain, acute injury or critical medical events and maintaining astronaut physical performance are critical issues for space agencies (Weber, 2020, private communication). Therefore, space agencies, such as the European Space Agency (ESA), have identified a need for more effective post-flight rehabilitation aimed at restoring optimal spinal posture and function (Bailey et al., 2018; Chang et al., 2016; Evetts et al., 2014) before astronauts venture beyond LEO. Due to the importance of spinal health in astronauts, ESA has also sponsored three “Topical Teams” (or working groups) in recent years relating to spinal health, including a recent topical team on “Post-mission Exercise (Reconditioning)”, which recommended a need to:

“Conduct more crew focused research on adaptation processes of muscles to further knowledge and improve inflight [countermeasures] and post-flight reconditioning strategies, and place particular focus on trunk muscles (and their neuromuscular junctions) relevant to spine-specific reconditioning.” (Stokes et al., 2016, p. 6)

In a systematic review, Winnard et al. (2017b) reported that no countermeasure is successful in preventing spinal muscle deconditioning in simulated exposure to microgravity, with no studies published from the actual microgravity environment. There is, therefore, a specific need for a countermeasure intervention that can address spinal deconditioning in astronauts (Stokes et al., 2016).

This thesis' viewpoint is that research undertaken with a terrestrial LBP population is directly applicable to the astronaut population and vice versa. Spaceflight research can be used as an accelerated ageing and sedentary lifestyle model without confounding comorbidities (for example Hides et al., 2017; Vernikos & Schneider, 2010). Spaceflight-induced spinal offloading and subsequent extensor muscle atrophy seen in astronauts is thought to mirror some aspects of chronic non-specific low back pain on Earth (Hides et al., 2017). This suggests that research undertaken on Earth can benefit spaceflight and vice versa (Stokes et al., 2017). A potential explanation for spinal offloading, either due to spaceflight, a sedentary lifestyle or ageing, may lead to non-specific low back pain discussed in section 1.3.2.

1.1 Low Back Pain on Earth

Low Back Pain (LBP) is the leading cause of disability and lost working days in western Europe, with 15.5% of men and 14.5% of women aged between 0-100 years of age experiencing LBP (Hoy et al., 2014). The percentage of people experiencing at least one episode of LBP increases in working and older-age adults to 49-80% (Driscoll et al., 2014; Staal et al., 2002). In the UK, an estimated 6.6 million workdays were lost in 2017/18 due to musculoskeletal issues, with back health representing 40% of all workplace-related ill health (HSE, 2018). Improving rehabilitation outcomes for non-specific low back pain has been selected by the World Health Organisation as a priority research area in the Priority Medicines for Europe and the World Update Report (Kapla%%n et al., 2013).

Low back pain is notoriously challenging to treat due to its multifactorial nature, involving the neuromusculoskeletal system and broader psychosocial considerations (Foster et al., 2018). Despite current research into LBP treatment, there is still a need for evidence-based, cost- and time-effective rehabilitation tools which can help to lower the burden of spinal issues worldwide. While considering the biopsychosocial model of healthcare, which aims to consider the whole person, this thesis will focus mainly on a biological element of a subset of LBP, specifically chronic non-specific LBP. Chronic non-specific LBP is pain or stiffness from the lower costal margin to the gluteal fold, with or without radiating symptoms, not attributed to a known pathology that lasts 12 weeks or more in a single episode (Staal et al., 2002). Around 90-95% of reported back pain is non-specific in nature (Oliveira et al., 2018; Staal et al., 2002).

1.2 The Spine and Motor Control Theory.

There are multiple approaches currently used to treat LBP, including exercise, manual therapy, education and psychological support (NICE, 2016). Exercise is one treatment that effectively reduces pain and disability in chronic non-specific LBP (Airaksinen et al., 2006; Hayden et al., 2005b; Koes et al., 2010). A Cochrane review in 2016 determined that Motor Control Training and general exercise were equally effective (Saragiotto et al., 2016), and, therefore, clinicians can pick their approach based on the patient’s needs. The European Space Agency has selected motor Control Training as its treatment of choice for post-flight spinal muscle reconditioning (Hides et al., 2016; Hides et al., 2021; Lambrecht et al., 2017). The theoretical and practical application of current Motor Control Training and its underlying assumptions about spinal stability are discussed below.

1.2.1 Spinal Stability

The concept of spinal stability was posited by Bergmark (1989), followed by a model of spinal stability by Panjabi (1992), in which three interconnected systems controlled the movements of the spine. These are the active, passive and neurological systems, representing the musculotendinous, osteoligamentous and nervous systems, respectively (Figure 1.1). Hoffman and Gabel (2013) expanded the Panjabi (1992) model to include spinal mobility and stability as the ideal spinal homeostasis, as evidence was lacking that stability alone can prevent LBP. In the expanded model, a dynamic version of each sub-system runs in parallel to the stability system. The task undertaken determines which subsystems dominate, although all subsystems are equally important (Hoffman & Gabel, 2013). When the sub-systems are not synergistic, the person is more likely to experience difficulties when faced with unexpected challenges to stability, which, left untreated, may lead to musculoskeletal disorders (Hoffman & Gabel, 2013).

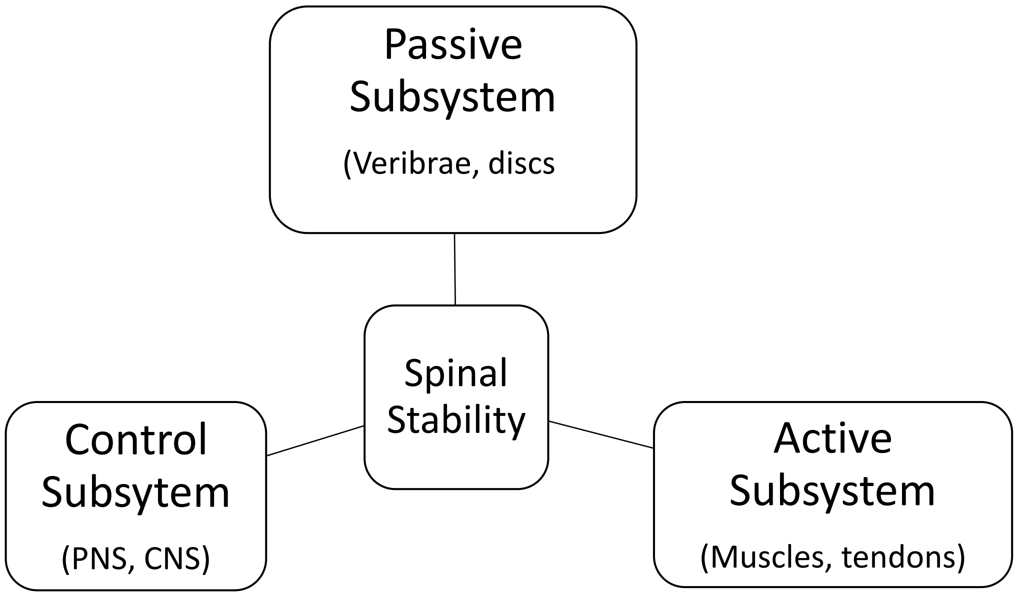


Figure 1-1 The Panjabi (1992) model of spinal stability with three subsystems.

1.2.2 The Spinal Stability Model and Chronic Non-Specific Low Back Pain

Chronic non-specific low back pain is a broad-spectrum disorder that is multifaceted, making its exact aetiology challenging to determine (Krismer & Van Tulder, 2007). However, microgravity induced deconditioning-related LBP and chronic non-specific LBP on Earth present in very similar ways, with changes such as extensor muscle fibre transitioning from slow-twitch to fast-twitch fibre type, fatty infiltration of muscle tissue and muscle atrophy (Van Dieën, 2018), and may have similar aetiologies. Post-flight LBP is likely to be multifactorial (Laughlin et al., 2015), however deconditioning of lumbopelvic muscles, such as Lumbar Multifidus (LM) and

Transversus Abdominis (TrA), seem to have a key role to play in the resolution and prevention of microgravity induced deconditioning-related LBP (Bailey et al., 2018; Harrison et al., 2018; Hides et al., 2016; Hides et al., 2008). It will therefore be the focus of this thesis.

The Spinal Stability model posited by Panjabi (1992) and Hoffman and Gabel (2013) offers one explanation of the theoretical link between altered motor control and LBP:

1. An injury occurs in a spinal tissue; this may be due to long-term micro-trauma, for example, due to poor posture or acute injury.
2. The neural control system now receives faulty mechanoreceptor signals during dynamic spinal loading due to injury.
3. The motor control unit compares the received signal with the expected signal and finds a mismatch due to the corrupted data; therefore, the output signal to the active stability system (muscles and tendons) is also incorrect.
4. The corrupted signal produces altered activation in the deep spinal muscles in response to the ‘fake’ dynamic load, leading to abnormal activation and timing, which no longer matches the real-world requirements.
5. The altered mechanics and activation patterns cause further signal corruption in the returning signal to the motor control unit, and the signal mismatch is amplified.
6. Each time the corrupted feedback loop is activated during dynamic loading, the signal mismatch increases, leading to a higher chance of segmental instability, increased abnormal tissue loading and stresses, and an increased neutral zone as the produced muscle activation moves further away from the real required output

7. Inflammation is triggered by the overloaded tissue around the unstable segment, which produces further nociceptive signals.

Hodges et al. (2013) expressed this theoretical pathway in detail, considering both feedforward, motor planning, and feedback, such as mechanoreceptor position. In the Hodges et al. (2013) pathway, disuse atrophy, fatty tissue infiltration, loss of stiffness and stability and psychosocial factors, such as fear of movement, are also considered. Supporting Hodges' model, Ferreira et al. (2004) found that TrA activation was delayed during upper limb tasks in LBP patients compared to healthy participants, suggesting that people with LBP have a mismatch between the actual and perceived muscle activation requirements for the task.

1.2.3 Lumbar Multifidus

The Multifidi muscles are the innermost of spinal muscles at every vertebral level, spanning between two and five vertebrae (Drake et al., 2005). The fibres of Lumbar Multifidus (LM) span from the sacrum, the origin of Erector Spinae, Posterior Superior Iliac Spine and mammillary processes to the spinous processes of caudal vertebrae (Drake et al., 2005; MacDonald et al., 2006). They have the largest cross-sectional area of any muscle in the lumbar region (Figure 2). The LM is a spinal extensor, able to produce roughly 60 N of extension force over its length (Ward et al., 2009), and is believed to have a key role in maintaining spinal stability (Ward et al., 2009). Lumbar Multifidus appears to be particularly vulnerable to deconditioning due to its specialised architectural features, such as short working sarcomere length which sit in the ascending and plateau region of the length-tension curve (Ward et al., 2009). In microgravity, the body relaxes into the neutral body posture with a flattening of the lumbar lordosis (Andreoni et al., 2000), placing the LM sarcomeres in a lengthened and potentially less effective position for contraction (Ward et al., 2009).

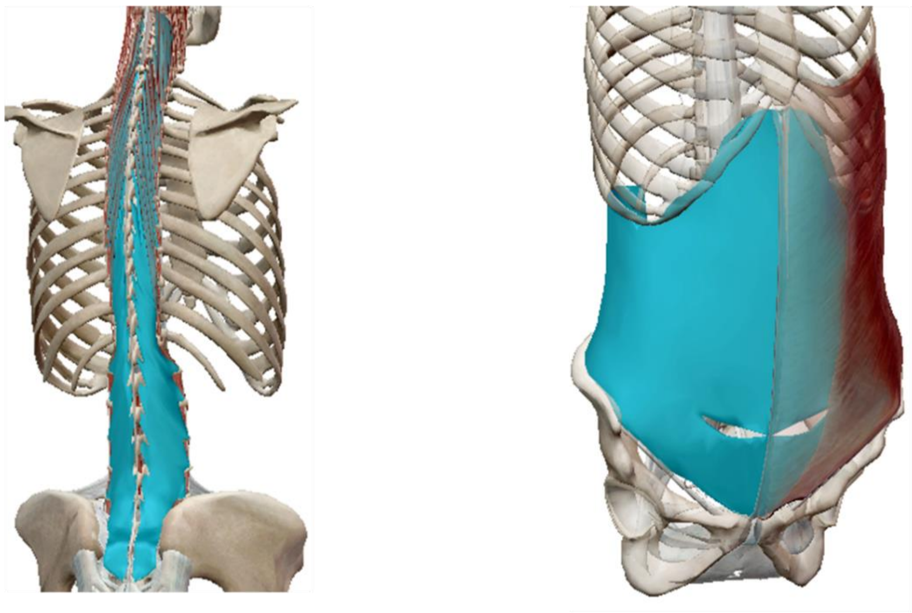


Figure 2 3-D anatomical model showing the position of the Multifidus and Transversus Abdominis muscles.

1.2.4 Transversus Abdominis

Transversus Abdominis is the deepest muscle of the anterolateral abdominal wall (Figure1). It acts like a corset around the abdominal viscera, raising intra-abdominal pressure and tensioning the thoracolumbar fascia, indirectly providing stability to the lumbar spine, and works in conjunction with LM to stabilise the spine (Hodges & Richardson, 1996; Kim et al., 2013). Transversus Abdominis originates from the iliac crest, the lateral third of the inguinal ligament, the thoracolumbar fascia and the lower six ribs, and inserts into the abdominal aponeurosis (Ward et al., 2009).

1.3 Current Motor Control Training

Bergmark (1989) described spinal muscles as either having a local or global role in spinal stability. The local muscles, which include the deep extensor muscles, like LM, are located close to the spine and mainly work as postural stabilisers at an intersegmental level. The global muscles include those anatomically further from the spine and not directly attached to it. They provide some stabilisation role, but their primary task is trunk movement and load spreading. An example of a global muscle is the Rectus Abdominis muscle (Bergmark, 1989; Jull & Richardson, 2000; O'Sullivan, 2000). The deep spinal muscles appear to be at particular risk of deconditioning in LBP and when chronically offloaded, such as long-duration bed rest and during spaceflight (Hides et al., 2011).

Motor Control Training is a progressive exercise programme in which the participant relearns how to correctly activate their deep spinal stabiliser muscles and then return to normal posture and function (O'Sullivan, 2000). There are three rings to the current approach to Motor Control Training; the first requires the isolation and activation of the deep spinal muscles in an offloaded position, for example, by performing an Abdominal Drawing-in Manoeuvre (ADIM) in the supine position. To assist the participant in locating and activating the target muscle, biofeedback, such as ultrasound imaging, can be used(Hides et al., 2008). Once the participant can activate the target muscles, they are progressed to more functional exercises such as limb extension from four-point kneeling. During this stage, the participant needs to focus on muscle activation and maintain a neutral spinal posture. The third stage returns to normal functional activities while maintaining a neutral spinal posture with minimal specific attention to muscle activation (O'Sullivan, 2000).

The stages of the current Motor Control Training approach are shown in Figure 1.2.

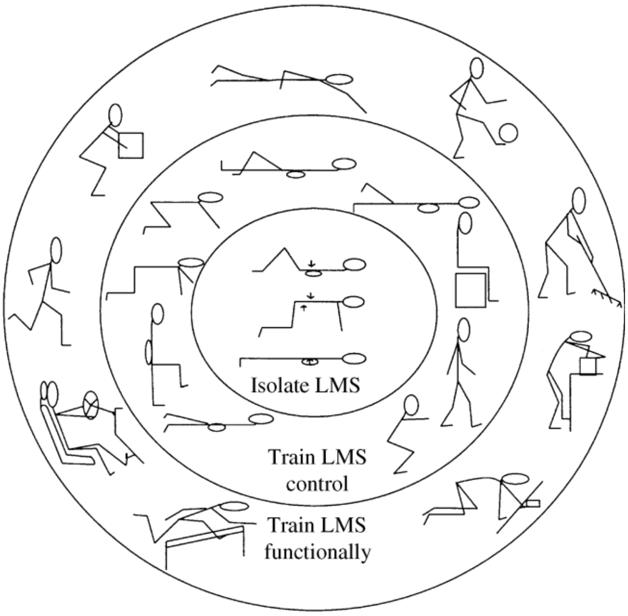


Figure 1-3. shows the ringed Motor Control Training tiers, taken from O'Sulliven (2000)

One of the main disadvantages of the current approach to Motor Control Training is the need for biofeedback and extensive therapist input (Debuse et al., 2013). Stage two exercises alone can take up to six weeks to teach and master (O'Sullivan, 2000). This is longer than the 21 days of post-flight rehabilitation period used by the European Space Agency (Lambrecht et al., 2017), potentially meaning astronauts return to active duties without fully recovering from microgravity-induced deconditioning. Within a terrestrial healthcare setting, the need for extensive therapist input may limit treatment options due to high service demands. For example, in 2018-19, physiotherapy was the third-highest accessed outpatient service in England, behind Ophthalmology and Trauma and Orthopaedics (NHS Digital, 2019) with 5.2 million outpatient appointments, representing 5.5% of all NHS outpatient appointments (NHS Digital, 2019). As such, the development of new approaches to the rehabilitation of spinal musculoskeletal deconditioning for astronauts and LBP could be beneficial.

1.4 The Functional Re-adaptive Exercise Device

The Functional Re-adaptive Exercise Device (FRED) has been under investigation since 2009 as a potential exercise intervention for rehabilitating people with chronic non-specific LBP and astronauts post-flight. It fits into the Motor Control Training paradigm by providing a targeted exercise for the deep paraspinal muscles (Caplan et al., 2014), which aims to reduce reconditioning time and need for therapist input by introducing weight-bearing motor control exercise, with functional limb movement from the start of the reconditioning process. (Caplan et al., 2014; Debuse et al., 2013; Gibbon et al., 2013; Weber et al., 2017; Winnard et al., 2016; Winnard et al., 2017, Winnard et al., 2017a). FRED exercise is described in detail below.

FRED is a modified elliptical trainer with the near-frictionless movement of the footplates (Figure 1.2). The exercise device provides a postural challenge in which the user is required to control the movement velocity and maintain a stable upright posture (Caplan et al., 2014; Debuse et al., 2013; Gibbon et al., 2013; Winnard et al., 2016; Winnard et al., 2017, Winnard et al., 2017a).

Figure 1-4 shows a user on the Functional Re-adaptive Exercise Device (FRED)

The FRED now has a base of fundamental research that supports its ability to recruit the deep spinal muscles automatically, specifically LM and TrA (Caplan et al., 2014; Gibbon et al., 2013; Weber et al., 2017; Winnard et al., 2017, Winnard et al., 2017a). The walking-type gait of FRED exercise was found to be effective at encouraging more tonic muscle activation patterns compared to overground walking, which more closely resembles the postural role of TrA and LM (Caplan et al., 2014; Weber et al., 2017)

FRED exercise appears to require more lumbopelvic control than over-ground walking, with a reduced transverse plane range of movement, suggesting FRED can locally recruit the lumbopelvic muscles at the segmental level (Caplan et al., 2014). Winnard et al. (2017a) and Gibbon et al. (2013) found that FRED exercise increases the lumbopelvic anterior tilt, which may place TrA and LM in a more advantageous position for activation. The ability to maintain neutral spinal curves is a key treatment goal of Motor Control Training (Hides et al., 2008; O'Sullivan, 2000). Another is the ability to progress the exercise as motor learning occurs (O'Sullivan, 2000). FRED exercise can be made progressively harder by increasing the footplate amplitude, which increased the footpath and total hip excursion, thus increasing the exercise demands to maintain a stable posture (Weber et al., 2017; Winnard et al., 2016).

FRED exercise has also been shown to encourage spinal extensor activation (Caplan et al., 2014); therefore, FRED may help counter the flexor-dominant muscle activation patterns seen in post-flight astronauts (Andreoni et al., 2000; Buckey, 2006). While FRED has been shown to activate LM and TrA appropriately under laboratory conditions, it has not yet been used as a treatment modality in symptomatic patient or astronaut populations.

There are several potential benefits of FRED exercise over conventional Motor Control Training. Firstly, the automatic activation of the deep spinal stabiliser muscles in a tonic anti-gravity pattern may reduce the need for intensive therapist-led treatment. Winnard et al. (2017a) showed that FRED posture stabilises within three minutes of FRED use, suggesting that most people will need minimal training to use FRED effectively. The potential to achieve effective rehabilitation in a shorter timeframe compared to contemporary Motor Control Training would be advantageous in both Terrestrial and astronaut healthcare where patients have limited reconditioning time available. Once trained to use FRED safely and effectively, patients will potentially use the device with minimal supervision, encouraging a self-management approach to LBP (NICE, 2016).

Furthermore, the weight-bearing limb movements of FRED provides a more dynamic and functional type of exercise (Debuse et al., 2013) compared to the mostly static, often single limb exercises used with the current Motor Control Training approach (O'Sullivan, 2000). All these factors suggest that FRED exercise may be an appropriate reconditioning intervention for terrestrial LBP patients and the astronaut population. The astronauts themselves, however, also need to be considered when designing new health interventions and demonstrating their efficacy, which is notoriously difficult to do in space health research because of crew availability and access. The following section presents one potential approach for including the astronaut's voice in space health research.

1.5 Balance and Low Back Pain

As well as negatively effecting quality of life (Hoy et al., 2012), people with low back pain are more likely to have difficulty maintaining their balance (da Silva et al., 2018; Mok et al., 2004), with LBP identified as an independent risk factor for falls (Frost & Brown, 2016). Falls may increase in people with LBP because, compared to healthy controls, people who experience LBP have delayed muscle activation (Radebold et al., 2001) and altered muscle pattern activation, loosing or reducing anticipatory activation prior to movement initiation, when responding to a balance perturbation (Frost & Brown, 2016). One example of muscle activation pattern change is moving from an anticipatory activation to a reactionary activation in the presence of pain (Hodges et al., 2003). Additionally, some people with low back pain may adopt a braced or guarded posture (van der Hulst et al., 2010), in which the spinal muscles are in a tonically active state and spinal stiffness is increased (Reeves et al., 2006). Due to this overactivity, the muscles are less able to react to a perturbation, and some research suggests that people with LBP may have to expend more energy even in quiet standing compared to healthy controls (Oyarzo et al., 2014). Because of the increased risk of falling after a balance perturbation, and the associated increase risk of injury (Marshall et al., 2016), it is important to understand how balance changes following periods of deconditioning, such as following spaceflight, can be rehabilitated.

For future Martian exploration missions a number of factors will negatively affect the crew, such as multi-system deconditioning (muscle, bone, circulation, vestibular etc (Williams et al., 2009))

Adding operational consideration for future planetary missions, such as walking while wearing spacesuit on Mars (Stuster et al., 2018), and the increased risks that a fall would pose to astronauts when they are unable to access medical assistance during surface exploration. Additionally, minimising falls risk may be an important objective in planning for planetary exploration missions following a period of deconditioning during the transit flight (Evetts et al., 2014; Stokes et al., 2016).

1.6 The astronaut-patient

Stokes et al. (2016) state that neuromusculoskeletal space research should include “more crew-focused research…on adaptation, processes to improve inflight [counter measures] and post-flight reconditioning strategies (Stokes et al., 2016, p. 6). Patient-centred care is expected in LBP research in terrestrial populations, e.g. Cooper et al., (2008), and forms a Core Quality Assurance standard of practice for Chartered Physiotherapists in the UK (CSP, 2013). No previous research has been identified that explores the astronaut perspective of low back pain and spinal deconditioning during or following spaceflight; therefore, the astronaut's voice has been silent in human spaceflight research, which favours quantitative over qualitative research approaches. Ease of access to crew and limitations on astronaut time may be one reason for this.

One way around the issue of crew access is to use the astronauts’ autobiographies so that the experience of microgravity-related and re-adaptation back pain is represented in their own words. While this approach lacks the finesse and specificity of targeted questionnaires, it allows astronauts to be represented in the research process in an easily accessible fashion. Ten autobiographies, two private communications and one news presentation from seven NASA, two ESA, one Canadian Space Agency and one Russian Space Agency, crewmembers were used as a point of reference. These covered 20 Space Shuttle flights and seven Soyuz flights (two to Mir and five to ISS). One mission, STS-100, was reported by two separate crewmembers. Four autobiographies did not mention any back pain (Jemison & Miles, 2001; Melvin, 2017; Sharman & Priest, 1993), although one did discuss whole-body and joint pain upon return to +1Gz (Kelly, 2017). The other six autobiographies, two personal communications and one news report specifically mention the crewmembers' experience of back pain either in space or upon return to Earth, which suggests it forms a significant enough experience to be worth reporting as part of their spaceflight story.

In-flight pain in the early adaption phase between flight day 0 to around flight day 7 (Kerstman et al., 2012; Pool-Goudzwaard et al., 2015) is mentioned in four autobiographies and one news report and has been described as 'significant…fierce backache' (Mullane, 2007, p. 174) which may affect appetite and mood (Jones, 2016). This type of pain is ordinarily self-limiting and has a minimal operational effect because it occurs during general microgravity adaptation, which is accounted for in operational planning (Kerstman et al., 2012; Pool-Goudzwaard et al., 2015).

An arguably more important symptom, and one which is the focus of this thesis, is pain experienced post-flight. It is crucial because it impacts the astronauts' ability to undertake their daily life, reduces their operational effectiveness and potentially leaves them exposed to longer-term health issues as they age. Post-flight pain is often described as resulting from the "crunching" (Massimino, 2017), "crushing" (Kelly, 2017), or "drag" (Hadfield, 2015) of gravity. Massimino reported this sensation as being "out of sorts", with another typical report being the length of time taken to recover after a long duration flight. Hadfield suggested that his recovery took months post-flight:

> "after elongating in space, my spine was now compressing again, so my lower back was constantly sore. I was surprised how long it took for these side effects to go away. Months later my (feet and) back were still complaining - frequently loudly- about what a drag gravity is." (Hadfield, 2015, p. 270).

While Peake wrote:

> "...if I picked up a heavy suitcase I could tell my core stability had deteriorated. It took about two months until my core strength felt completely normal again" (T Peake, 2017, pp. 230-231)

after a long-duration mission in 2016. Massimino (2016) also reported dropping shopping bags in the early post-flight period, suggesting that the post-flight issues are widespread.

These reports are relevant because they show that even with the current in-flight exercise countermeasures, spinal deconditioning is not adequately addressed. It also identifies a significant post-flight period, even with rehabilitation, in which the astronauts perform suboptimally. Maintaining astronaut performance is a significant concern for space agencies (Weber, private communication, 2020). Interestingly, back pain was reported across space agencies and launch vehicle types, suggesting that no one space agency has solved the issue. This may be of more significance in the future when astronauts are required to perform independently on planetary exploration missions without the support of reconditioning and medical staff.

One astronaut, who asked to remain anonymous, reported that their post-flight spinal injury required corrective surgery. It caused significant disability and pain. The injury pattern was unusual in +1Gz and may have been down to their repeated exposure to high-G loads and the strenuous activity required during multiple spacewalks (Anon astronaut, private communication 2020). However, current literature has not specifically identified extra-vehicular activity (EVA) as an independent risk factor for spaceflight related spinal injury. Massimino (2017) and

Parazynski and Flory (2017) both mention that their height was a factor in their roles as spacewalkers, and both reported gaining more than the allotted one inch of additional height while wearing their spacesuits, which suggests that height may be a non-modifiable risk factor for spinal pain in space-walkers, although research is needed to confirm this.

Finally, Parazynski and Flory (2017) highlighted that the astronaut population is ageing, and the additional risk factor of age after spaceflight means the astronaut experiencing “spinal trouble is almost inevitable as an overloaded, rickety Jenga tower toppling over into a ragged heap” (Parazynski & Flory, 2017, p. 3). By focusing research efforts on the prevention and rehabilitation of post-flight spinal issues, not only will future spacefarers be healthier, but those with previous spaceflight experience could also age with healthy spines after they retire from flight status.

Using the astronauts’ own words, this section aimed to show that spaceflight-related spinal pain is a distressing experience that impacts real people’s daily lives, even when they are part of a small, highly select, professional group. Spaceflight-related back pain can be experienced early inflight as part of the adaptation process known as Space Adaptation Back Pain (SABP) or post-flight as part of the re-adaptation period following deconditioning. Space Adaptation Back Pain is discussed below, and post-flight pain is discussed in detail in chapter 2 as part of the literature review.

1.7 Space Adaptation Back Pain

Space Adaptation Back Pain (SAPB) occurs as the body adjusts to the microgravity environment and is specific to spaceflight. 52-56% of astronauts experience this type of LBP, often described as mild-moderate aching or stiffness in the lumbar spine (Kerstman et al., 2012; Pool-Goudzwaard et al., 2015). Novice and female astronauts are at a slightly increased risk of SABP, although as most symptoms are mild-moderate, the operational risk is low (Kerstman et al., 2012). Symptoms generally appear by flight day 2 (FD2) and have subsided by FD5, although during this period, analgesics and the foetal tuck stretch (where the knees are brought up to the chest) may be required to ease the discomfort (Kerstman et al., 2012).

Possible sources of SABP are the zygapophyseal joint capsule stretching or hyperhydration of the intervertebral disc (IVD) in-flight due to cephalic fluid shift (Freeman et al., 2010; Sayson & Hargens, 2008). Initially, it was thought that microgravity-induced spinal lengthening was due to increased IVD hydration and subsequent increase in disc volume (Belavý et al., 2015; Sayson & Hargens, 2008). However, recent detailed studies into this phenomenon suggest that the change in spinal length is probably due to a combined effect of IVD height change and a flattening of the spinal curves due to LM atrophy (Harrison et al., 2018) with a spinal shape having a more significant role than that of IVD swelling (Chang et al., 2016; Green & Scott, 2018; Sayson & Hargens, 2008).

In-flight activities such as exercise are another risk factor for developing back pain in space. Wotring (2015) retrospectively assessed medication use by 24 US astronauts over 20 missions and found that 40% of back pain requiring medication, normally ibuprofen or paracetamol, was associated with the use of the Advanced Resistive Exercise Device (ARED) and one episode of SABP. Non-prescribed medication use is not routinely monitored on ISS, and only instances where medication use was mentioned in the Lifetime Surveillance of Astronaut Health were included. Therefore, due to the methodology used, actual painkiller use for back pain and exercise-related back pain may be higher.

While medication use was low, preventing back pain and spinal injury is essential to ensure that astronauts can maximise their work capacity while on ISS. This can be achieved with regular teleconferences with exercise specialists, ensuring that proper training techniques and posture are used when exercising, especially on ARED (Petersen et al., 2016). On deep space missions to Mars, where the communications delay will make this difficult, if not impossible, the astronauts must be able to train safely and independently. Therefore, future research should consider making exercise safer, easier to self-monitor and adjust so that the crews can maintain their own health in-flight while reducing consumables such as medication that may be required for the return journey (Laws et al., 2020). Overall, SABP appears to be an unavoidable consequence of the microgravity adaptation process. Spinal deconditioning occurs later due to offloading (Harrison et al., 2018 and Bailey et al.,2018) and does not appear to be symptomatic in-flight, although ARED exercise does pose a risk of spinal injury when deconditioned. Maintaining spinal health in-flight is essential to minimise injury risk during exercise and EVAs and allow a safe, functional return to gravity.

1.8 The Aims and Objectives of this Thesis

The European Space Agency has shown an interest in using FRED as a post-flight reconditioning tool. However, further research is needed using FRED over longer time scales with patient populations before being used post-flight in

astronaut populations. This thesis aims to bridge the gap between the proof-of-concept research previously carried out on FRED and future hypothetical operational use with astronauts while considering FREDs possible use in terrestrial back pain treatment. This transitional research need will be addressed with two exercise intervention studies, the first looking at the symptomatic LBP population of working-age adults. The second uses the head-down-tilt bed rest model to study the effects of FRED exercise during the reconditioning period following simulated spaceflight.

The aims of this study are, therefore, to:

- Determine the influence of FRED exercise intervention on lumbopelvic muscle size, patient-reported function, pain, movement control and balance in a chronic non-specific low back pain population to determine whether FRED is a suitable rehabilitation intervention in symptomatic populations (LBP study).
- Investigate the effects of a FRED intervention on paraspinal muscle structure, low back pain and movement control after 60-days of head-down-tilt bed rest, simulating the deconditioning effects of long-duration exposure to simulated microgravity (AGBRESA Study).

The specific objectives for the LBP study, looking at chronic LBP in a working-age population, are set out in table 1.1, and the specific objectives for the AGBRESA study, looking at spinal deconditioning following 60-day 6º head-down tilt (HDT), are shown in table 1.2.

Table 1-1. Specific objectives for the LBP study

Objective number	Examine whether 6-weeks of FRED exercise:	Chapter
1	reduces mechanical LBP	4
2	affects the analgesic intake and the rate of change of pain	4
3	affects the physical activity level of individuals with LBP	4
4	affects the wellbeing and everyday function in people with LBP	4
5	affects the LM CSA and thickness	5
6	affects the TrA thickness at rest and approximate working maximal voluntary contraction	5
8	improves functional and static balance in people with LBP	6

Table 1-2. Specific objectives for the AGBRESA 60-day Head-down-tilt bed rest study.

Objective number	Examine whether FRED exercise following 60 head-down bed rest;	Chapter
9	reduces HDBR induced mechanical LBP	7
10	affects the LM cross-sectional area	8
11	affects the TrA thickness at rest, working and maximal contraction	8
14	improves functional and static balance following spinal deconditioning	9

1.9 Thesis overview

The aims of the thesis will be achieved through the following chapters:

Chapter One will introduce LBP in astronaut and terrestrial populations and discuss the theoretical underpinning of FRED exercise.

Chapter Two will provide a narrative literature review of in-flight countermeasures, post-flight reconditioning and simulated space flight findings.

Chapter Three will detail the methodology shared between both studies, including Transversus Abdominis and Lumbar Multifidus ultrasound imaging, FRED exercise and balance tasks.

Chapter Four will discuss the results of the Patient-Reported Outcome Measures of Terrestrial adults with chronic non-specific low back pain (LBP study)

Chapter Five will discuss the LBP study ultrasound imaging (USI) results for the TrA and LM muscles.

Chapter Six will present the LBP study static balance data and FRED movement variability data following six weeks of FRED exercise intervention.

Chapter Seven will be the first chapter considering the AGBRESA study; it will discuss participant-reported pain symptoms associated with 60-days head-down tilt bed rest and post-bed rest reconditioning.

Chapter Eight will discuss the LM and TrA morphological changes seen in the AGBRESA study, using USI and MRI, both after bed rest and following 13 days of FRED exercise.

Chapter Nine will explore static and dynamic movement control changes following bed rest and 13 days of FRED exercise.

Chapter Ten will draw the overall conclusions of this thesis together, identifying the original contribution that it makes, limitations of the research and future directions.

2 Chapter 2 In-flight exercise countermeasures and post-flight reconditioning for spinal health in astronauts: what have we learnt from microgravity and microgravity analogue studies?

Microgravity has wide-ranging deleterious effects on the human body (Gradwell & Rainford, 2016). Specific exercise countermeasures and reconditioning interventions are necessary to maintain operational effectiveness and reduce injury risk in astronauts (Stokes et al., 2016). Space-based research may also have transferable knowledge to broader terrestrial patient populations (Stokes et al., 2016). This thesis considers in-flight countermeasures in two epochs; those before 2009, including the Interim Resistive Exercise Device (iRED) and those after 2009, which use the Advanced Resistive Exercise Device (ARED). Because of the fundamental change in countermeasure provision after the introduction of ARED, this narrative review will only consider countermeasures from 2009 onwards.

The Advanced Resistive Exercise Device (ARED) entered service in 2009 (Loehr et al., 2015), and in-flight countermeasures Pre-ARED training consisted of low-load exercises using devices such as bungees and the Interim Resistive Exercise Device (iRED). ARED provides loads of between 2.2 to 272 kg, allowing for high-load exercise and progression throughout long-duration missions (Petersen et al., 2016). iRED could provide workloads between 5 to 136 kg (Petersen et al., 2016). Pre-flight bodyweight needs to be added to training loads in microgravity (Hackney et al., 2015; Loehr et al., 2015), and iRED could not provide an effective training load once bodyweight was accounted for. Overall, countermeasures before 2009 were not successful in maintaining muscle strength (Petersen et al., 2016). With the installation and regular use of ARED in 2009, the modern era of in-flight exercise countermeasures began. Astronauts now return to Earth in a generally good condition (Petersen et al., 2016), although deconditioning of specific muscle groups, such as Lumbar Multifidus (LM), still needs to be addressed (Bailey et al., 2018; Chang et al., 2016; Hides et al., 2016) particularly at the L5 level (Hides et al., 2016).

This literature review aims to summarise current knowledge on post-spaceflight (actual and simulated) changes in lumbopelvic muscle and spinal health. It will also compare the in-flight exercise countermeasure and post-flight reconditioning programmes of the three main space agencies: the National Space and Aeronautics Administration (NASA), the European Space Agency (ESA) and the Russian Space Agency (RSA), to elucidate gaps in knowledge and points for future research.

2.1 Risk factors for spinal injury during or following spaceflight.

Space missions are complex; astronauts have various roles to complete at different timepoints, some of which may increase the risk of spinal injury. For example, at launch, astronauts experience elevated Gx load (Gradwell & Rainford, 2016) (Figure 2.1), vibration and acoustic pressure for several minutes (Arenas & Margasahayam, 2006). During re-entry, astronauts experience high vibration levels, sustained Gx loading and a potentially high impact during Soyuz landing (Gradwell & Rainford, 2016). Gz loading is also experienced when using ARED for up to 60 min (Loehr et al., 2015; Petersen et al., 2016). This variable environment means that an astronaut will experience brief periods of high-intensity loading throughout their mission while in a deconditioned state and, thus, may become more prone to spinal injury (Green & Scott, 2018).

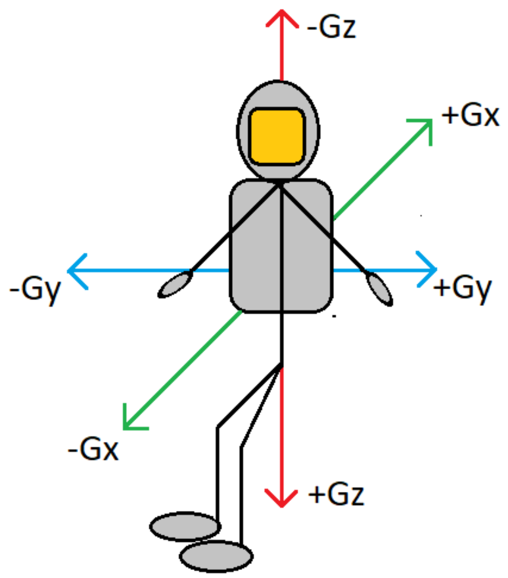


Figure 2.1. Naming Conventions for Acceleration Forces, adapted from Ernsting's Aviation and Space Medicine 5th edition. When considering the acceleration forces affecting the body this thesis will use the standard aerospace medical convention of reporting resultant forces using a triaxial coordinate system, in which the z-axis runs longitudinally, parallel with the spine, from head to foot, the y-axis runs mediolaterally, from right to left, and the x-axis runs anteroposteriorly, from front to back. (Gradwell & Rainford, 2016)

In-flight activities, like exercise countermeasures (Scheuring et al., 2009) and extravehicular activities (Strauss, 2014), may have an increased injury risk because the astronaut is required to do work and carry a load in a potentially deconditioned state (Chappell et al., 2017). On ISS, ARED countermeasure and EVA-related pain were both identified as leading causes of analgesic use in-flight (Wotring, 2015). On future planetary exploration missions, this risk may be more important as astronauts may be undertaking surface EVAs for up to 24 hours a week, including around 10% of that time doing heavy physical labour or challenging activities such as a suited 'walk back' of up to 10km (Chappell et al., 2017). Interestingly, although current research has identified that trunk injuries account for roughly 3% of EVA-related musculoskeletal injury (Strauss, 2014), no research was identified which compared EVA and non-EVA crew injury occurrence to determine if EVA is a risk factor itself for spinal injury, as suggested by Parazynski and Flory (2017).

Landing is the next high-risk situation for the crew (Caldwell et al., 2012). Soyuz landings have led to hospitalisation for back injuries (Kim, 2008). Currently, the main way to return to Earth from the ISS is by Soyuz spacecraft (NASA, 2020), which, unlike the Space Shuttle, involves a hard landing in the Kazakh Steppe (Gradwell & Rainford, 2016). For future missions, including those to the Moon and Mars, NASA has chosen two commercial spacecraft which will also use a capsular design: Boeing's CTS100 Starliner, which is designed to land on land (Boeing, 2019) and SpaceX's Crew Dragon, which is due to splashdown on water, similar to the Apollo capsules (Crawley, 2020). Therefore, the commercial crew programme spacecraft are likely to have similar issues to Soyuz regarding acceleration forces on the body and potential injury.

The Soyuz landings have a transient peak load of +6Gx, and an average load of +3Gx for up to 10 minutes (Gradwell & Rainford, 2016). In a post-flight deconditioned state, astronauts are at a higher risk of injury (Caldwell et al., 2012; Johnston et al., 2010); therefore, crews are assisted when disembarking from the spacecraft and remain in a supported, seated position for medical checks (Peake, 2017). An example of this can be seen in Figure 2.2. Although in a normal Soyuz landing, the crews are assisted by Search and Rescue and medical teams (Rukavishnikov et al., 2014), in the case of an off-nominal landing, the crew must egress unassisted, such as in Expedition-6, where a ballistic re-entry led to the capsule landing 500km away from their intended landing site (Pettit, 2010) The crew were able to exit the vehicle safely. However, one crew member could not walk unaided and had to crawl to safety while awaiting rescue (Pettit, 2010). This experience is relevant to potential future exploration missions to other planetary bodies; upon landing, all crew members must function safely and independently to reduce the risk to themselves and the rest of the crew (Pettit, 2010; Stuster et al., 2018). Re-adaptation to the +1Gz environment places significant demands on the body, with the neurovestibular, cardiovascular and musculoskeletal systems affected, making returning to Earth more difficult than adapting to microgravity (Hides et al., 2016). Therefore, countermeasures are designed to mitigate microgravity induced deconditioning so that crewmembers can safely complete their mission tasks and transition back into a gravity environment (Febus, 2020a). In-flight countermeasures are discussed in more detail in the next section.

Figure 2.2 ESA astronaut Tim Peake with the Search and Rescue crew after landing being moved carefully in a seated position to reduce the risk of injury. Photo ESA 2016.

2.2 In-flight Countermeasures

Stokes et al. (2016) considered how to structure a successful planetary mission countermeasure program. Figure 2.3 demonstrates the ideal, current and least ideal physiological pathway an astronaut could follow, with and without in-flight countermeasures. Ideally, the countermeasure programme effectively maintains pre-flight fitness and function, with minimal detriment to health. Stokes et al. (2016)

identified that research is required to reach a multiagency consensus on pre-, in- and post-flight exercise and reconditioning to maintain and restore astronaut health. However, there are differences in how NASA and RSA approach their countermeasure programmes. This is reflected in the functionality of their training devices, discussed below, with a full outline shown in Table 2.3.

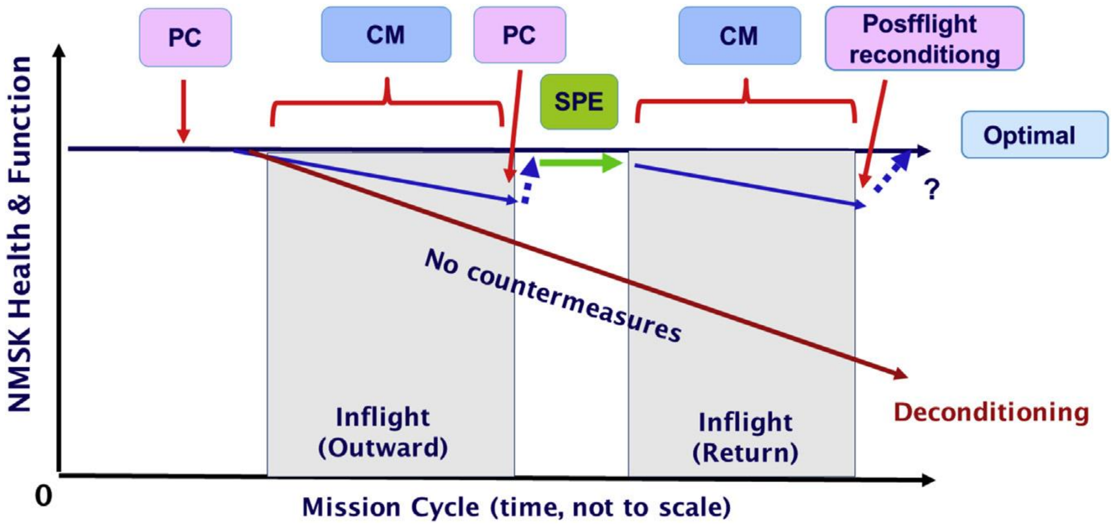


Figure 2.3. Maintenance of astronaut condition during one long-duration mission cycle from Earth to a planet (e.g. Mars), with surface exploration and back, taken from (Stokes et al.., 2016). PC = preconditioning CM = countermeasure SPE- time on surface.

2.2.1 Exercise Hardware on ISS

To minimise the impact of the microgravity environment on crew physiological systems, each space agency requires its crewmembers to engage in exercise countermeasure programmes that use a range of exercise hardware. The ISS is divided into the Roscosmos State Corporation for Space Activities (RSA) and US Operating Segments (USOS); astronauts have training equipment available within both. There are two treadmills on the ISS; BD-2 in the Russian segment and Treadmill with Vibration Isolation Stabilisation (T2) in the USOS, twocycle ergometers - VELO (RSA) and cycle Ergometer with Vibration Isolation System (CEVIS, USOS) - and on the USOS the Advanced Resistive Exercise Device (ARED) There are also non-mechanical training tools such as resistance bands and bungees. Russian crews also have access to axial loading 'pengvin' suits and electrostimulation as an adjunct to their active countermeasure programme; however, these are not widely used (Kozlovskaya et al., 2015; Loehr et al., 2015; Petersen et al., 2016). Exercise hardware location on ISS is shown in Table 2.1 below.

Table 2-1 Exercise Hardware on ISS in the USOS and RSA segments

Exercise type	USOS	RSA
Treadmill	T2	BD-2
Cycle ergometer	CEVIS	VELO
Resistance	ARED	
Adjuncts		Pengvin suit, Electrostimulation, Resistive bands and bungees

2.2.2 NASA and associated space agency countermeasure program

NASA, JAXA (Japanese space agency) and CSA (Canadian Space Agency) follow the same exercise countermeasure programme, which focuses on ARED and treadmill running, with the overall aim of minimising physiological adaptation to microgravity, and fully utilising training hardware (Loehr et al., 2015). The NASA programme aims for 90 minutes of resistive exercise and 60 minutes of aerobic exercise 6 days a week (Loehr et al., 2015). However, this time includes setting up, stowing and personal hygiene. Loads are increased throughout the flight based on performance (Loehr et al., 2015), aiming for a 5% increase every third session if the previous two sessions were completed satisfactorily (Hirsch, 2010). NASA uses a mixed training programme on a three-day cycle which includes powered treadmill running at 60-85% full body weight and a maximum speed of 16 km/h (Loehr et al.

2015), upper and lower body ARED exercises and cycle ergometry. The training programme utilises varying loads, repetitions, intervals and stances to provide a diverse programme; example exercises include squats, deadlifts, heel raise with 3-4 sets of 6-12 reps per exercise (Hirsch, 2010)

2.2.3 ESA in-flight countermeasure program

The ESA programme aims to maintain the overall fitness of the astronaut to above average for their age (Petersen et al., 2016). While functionally very similar to the NASA programme, the ESA programme is highly individualised, considering the astronaut's pre-flight fitness and personal preferences. ESA astronauts are scheduled to train seven days per week (Petersen et al., 2016). ESA astronauts are expected to complete 60 minutes of resistive exercise and 30 minutes of aerobic exercise each day. A resistive load is increased 3 to 5% each week, while the aerobic load is increased based on performance assessment (Petersen et al., 2016). The countermeasure programme is set up into 3 phases; adaptation from flight day (FD)1-20, which aims for 50%-60% maximal capacity, main phase from FD21 until roughly recovery (R)-30, or four weeks before landing, with training loads of up to 80% maximal capacity and harness loads of 70-80% full body weight (Petersen et al. 2016). Example exercises include 3-5 sets of 6-15 repetitions of (every day) squats, heel raises, deadlift, (variable) crunches, and bench press (Petersen et al. 2016). The final phase lasts about four weeks before re-entry, and cycle ergometry is dropped in favour of running and high-load ARED exercise (Petersen et al., 2016)

2.2.4 Russian Space Agency countermeasure program

The RSA programme supports overall functional capabilities, focusing on locomotion and posture (Kozlovskaya et al., 2015). The RSA program is structured around a 4-day cyclical high-intensity interval training programme that centres on using BD-2 in an unpowered running mode so that the cosmonaut is required to move the treadmill belt using foot-force. Upper-body resistance training and cycle ergometry, and the pengvin suit are secondary to the running intervention (Kozlovskaya et al., 2015), although some cosmonauts use ARED like their USOS colleagues (Kukoba et al., 2019). Cosmonauts train for up to 2.5 hours per day over two sessions, six days per week, and the program incorporates an active rest day, which the cosmonauts can use for training if desired (Kozlovskaya et al., 2015).

Kukoba et al. (2019) gave a detailed account of the actual training programmes carried out by five cosmonauts who undertook more than one long-duration flight to the ISS. Their study was the first to report the differences in bone mineral density for crewmembers who undertook flights before and after the introduction of ARED. It confirmed that the higher resistive loads provided by ARED are better able to ameliorate bone mineral density loss compared to the resistive exercise band, which can only provide up to 25kg of load. In the program, cosmonauts undertook resistive exercise every other day, interspersed with cycle ergometry and active or passive running. ARED training loads were between 100% Earth body weight and 240% Earth body weight in 3-4 sets of 12-26 repetitions. During the ARED period, crewmembers lost around 6% of the bone mineral density at the L1-L4 spinal level, although individual variation ranged between 0.8% and 15.4% (Kukoba et al., 2019). This finding suggests that on future planetary exploration missions, it would be beneficial to know which crew members were responders or non-responders to the available countermeasures so that the individual training needs can be considered. For example, two cosmonauts lost the same amount of bone mineral density regardless of the training modality, while three lost considerably more using resistive exercise bands. There may only be space for resistance band countermeasures in the confined space of the exploration spacecraft (Laws et al., 2020). Therefore, crewmembers who respond well to this type of exercise would be better candidates for that mission profile. This consideration becomes more important when combined with the modelled vertebral strength data by Burkhart et al. (2019), which shows that bone strength reduces by around 6% after a 6-month flight and is not regained at the four-year follow-up point. While fracture risk is low for normal activities, it increased into the moderate range for strenuous activities, suggesting that on a planetary mission requiring surface excursions or construction activities (Chappell et al., 2017) for extended periods, the astronauts may be at an increased risk of harm, particularly if they are in the exercise non-responder group.

Each agency has a different focus for its countermeasure programme: NASA/ESA focuses on daily ARED resistive exercises (Loehr et al., 2015), and RSA focuses on high-intensity interval training on the treadmill with resistive training every other day (Kozlovskaya et al., 2015). A detailed comparison of the training programmes is given in Table 2.3

Table 2-2 A comparison of the in-flight countermeasures used by the three main ISS partner Space Agencies.

	ESA	**NASA**	**RSA**
Aim of countermeasure program	Maintain overall fitness above average for age group	Minimise muscle and bone loss while maintaining performance and ensuring maximal hardware utilisation.	Support locomotor and postural function
Training type	Varied program with interval, hill, slope and constant training sessions	Varied program with interval and steady-state training sessions	High-Intensity Interval Training and Active rest
Main Hardware used	ARED/ TM	ARED/TM	TM (ARED)
Other hardware used	cycle ergometry	cycle ergometry	cycle ergometry, axial loading suit, electrostimulation and bungies
Total training time per day	2.5hr	2.5hr	2.5hr
Training sessions per day	1 or 2	1 or 2	2
Number of training sessions per week	7	6 (+1 if desired)	6 (+1 if desired)
training pattern	3-day rotation low, medium, high loads	3-day rotation high, medium and light loads	4-day rotation max, sub max moderate and light loads.
Resistive exercise time/day	60min inc. heel raises, squads and deadlift every session	1.5hr inc. 75%BW squats and heel raises every session	At least 30% total time as unpowered TM running
Progression	.+3-5%/ week in the main phase	increase every other week on performance	on performance of MO-3 fitness test

	ESA	NASA	RSA
aerobic exercise time/day	30min CEVIS 80% pre-flight max or higher or 30 min TM running	60min TM or CEVIS based on crew preference. TM includes 5min unpowered running	varies by day of cycle
Progression	on performance aiming for 80% or higher pre-flight max	on performance	on performance of MO-3 fitness test
Adaptation phase	FD1- 20, loads at 50-60% pre-flight max.	FD1-FD14	FD1-10, load <50% pre-flight max
Main Phase	FD21-R-30	FD15-R0	FD11 to R-30
Pre-return phase	R-30/ 15 to R-1, high resistive and TM loads, no CEVIS		R-30 to R-1, high intensity, and LBPN R-10- R-1.

To date, only Kokuba et al. (2019) have considered the overall efficacy of the in-flight exercise countermeasure programme for Russian crewmembers. No data could be identified from the ARED-era for USOS crew members or comparing RSA and USOS exercise programmes to each other, so it is impossible to determine which, if any, is more effective.

However, two recent reviews on terrestrial training suggest that the current in-flight exercise programs may not be as effective as intended. Jones et al. (2019) highlighted that concurrent training, in which both resistance and cardiovascular-type exercises are completed together, may inhibit muscle mass and strength production, both key aims of in-flight countermeasures (Febus, 2020a). In the RSA programme, resistive exercise is undertaken every other day, in contrast to the other space agencies, which has been reported to be as effective for maintaining bone mineral density as daily training (Kukoba et al., 2019), suggesting that reducing concurrent training is an appropriate way to optimise in-flight countermeasures.

Steele et al. (2019) suggested that exercise effort, independent of modality, may be more important in achieving physiological changes such as muscle hypertrophy. Therefore, High-Intensity Interval Training (HIIT), in which astronauts complete a single exercise-type with high or maximal effort, could be an effective countermeasure. HIIT is also supported by the findings of Jones et al. (2019). Jones et al. (2019) also suggested that treadmill running, even as HIIT, is not an effective countermeasure because it has high levels of training interference and that rowing or cycling would be more effective. Therefore, the RSA programme, and the pre-landing phase of the ESA programme, may be improved by changing HIIT treadmill running for HIIT cycle ergometry training, and the general USOS programmes could utilise CEVIS HIIT in place of the low and medium training days in the current programme, to be more effective. However, further research is needed to confirm this. On future Mars and Moon missions, single-modality HIIT would reduce the need for exercise hardware, particularly helpful in exploration-class vehicles in which training space is severely limited (Laws et al., 2020; Steele et al., 2019). However, further research would be needed to determine which single modality would be most effective and acceptable to the crew.

This section has considered inter-agency differences in exercise countermeasures and some potential confounding factors limiting countermeasure effectiveness, based on terrestrial exercise science. These considerations are important because researchers need to better understand current exercise prescription practices and inter-agency differences in countermeasure programmes to better interpret findings from space-based research, understand potential areas for further study, and provide improved operational information for future planetary exploration missions.

Additionally, in-flight countermeasures used on ISS are at least partially successful at maintain the prime mover muscle groups (Loehr et al., 2015; Petersen et al.,

2016) and lower limb bone mineral density (Kukoba et al., 2019) following the introduction of ARED in 2009. However, maintenance of the postural muscles, such as Lumbar Multifidus, has not been as successful and still needs to be addressed (Bailey et al., 2018; Chang et al., 2016; Hides et al., 2016). The following section will consider what is currently known about the lumbopelvic muscles in actual and simulated spaceflight.

2.3 Spinal Health after actual and simulated spaceflight

2.3.1 Spinal changes seen in microgravity.

Spinal muscle research has been undertaken in the astronaut population because back injury rates in astronauts are higher than their non-spaceflight peers (Johnston et al., 2010). Bailey et al. (2018) found that LM cross-sectional area (CSA), and functional CSA, measured using MRI at L3/4, reduced post-flight in five NASA astronauts by 6.2% and 14.2%, respectively. Unusually one astronaut also gained CSA post-flight. The astronauts also experienced a 40% decrease in spinal flexion-extension range of movement, which limited their post-flight function. Agreeing with Pool-Goudzwaard et al. (2015), Bailey et al. (2018) also found that post-flight LBP was strongly correlated with pre-existing spinal conditions or a history of LBP. The MR images were taken on Recovery (R)+ 1, so the crew had been re-ambulating at +1Gz for at least 24 hours. This timing means that any transient changes immediately post-landing, such as changes in disc height due to hyperhydration, may have been missed (Bailey et al., 2018).

As discussed earlier, the NASA in-flight countermeasure programme cannot prevent spinal postural muscle deconditioning, with Chang et al. (2016) reporting a 19% decrease in spinal extensor CSA. Following the NASA reconditioning programme, 68% of the muscle mass lost during spaceflight was recovered six weeks post-flight, suggesting that the NASA reconditioning programme partially successfully returned the astronauts to their pre-flight status. This study also found no change in intravertebral disc (IVD) height, although MR images were taken 24-48 hours after landing (Chang et al., 2016).

Two studies found that paraspinal muscle atrophy post-flight is linked to flattening of the lumbar lordosis, leading to an increased risk of LBP (Bailey et al., 2018; Harrison et al., 2018). In addition to these spinal morphological changes, Mulavara et al. (2018) found that postural control and stability as a whole was decreased in NASA astronauts following six months of spaceflight and bed rest participants following 70-days head-down tilt bed rest, despite an intense six (6) days/week resistance and cardiovascular exercise countermeasure being used throughout microgravity/ bed rest exposure. The loss of postural control and stability was particularly evident in functional tasks such as fall recovery and ladder climbing, both key functional activities (Stuster et al., 2018), which may be necessary for an emergency evacuation (Miller et al., 2018; Mulavara et al., 2018) or planetary landing scenario (Stuster et al., 2018). These findings suggested that the current NASA in-flight countermeasures are not effective at maintaining spinal postural muscle mass or postural control and that specific spinal postural control countermeasures are needed (Bailey et al., 2018; Chang et al., 2016; Mulavara et al., 2018).

In contrast to the NASA astronaut countermeasure programme, a case study of one ESA astronaut reported that the ESA in-flight countermeasures successfully maintained LM CSA between L1 and L4, but significant atrophy of around 29% was observed at the L5 level (Hides et al., 2016). However, this disagrees with the findings of Chang et al. (2016) looked at pre- and post-flight changes after long-duration missions in six NASA crewmembers. Although they measured all spinal extensor muscles as one unit, a 19% decrease in functional CSA was observed, suggesting that all spinal extensor muscles suffer atrophy in flight to some degree. However, caution must be taken when comparing results because Hides et al. (2016) utilised USI, while Chang et al. (2016) used MRI. Harrison et al. (2018) found that while USI was an appropriate imaging modality for use in space research, both in-flight and on the ground, the measurements were only weakly correlated to the MRI findings, and, therefore, each modality should be considered separately, thus making direct comparisons of muscle CSA in these studies inappropriate.

Additionally, Chang et al. (2016) looked at the paraspinal muscle cross-sectional area at the L3-4 level, whiles Hides et al. (2016) studied L5-S1, therefore, a direct comparison between the ESA and NASA findings are impossible. Low back pain research in clinical populations suggests that the L5-S1 level is more often affected in chronic LBP in terrestrial populations (Wallwork et al., 2009); this level may also be of more use than higher vertebral levels when looking at astronaut spinal deconditioning.

Hides et al. (2016) also found that microgravity exposure induced a flexor/extensor imbalance, with a flexor bias mirroring sedentary terrestrial population. Encouragingly, the ESA reconditioning programme increased the L4/5 LM CSA to greater than the pre-flight baseline after 14 days. However, it is very important to note that this study only represents one individual; therefore, it is not appropriate to extrapolate the results to the entire astronaut population. Only the individual astronaut's response to the training program can be assessed. Assuming the ESA astronaut corps shows individual responses to exercise in a distribution similar to the cosmonaut population, the findings of Kukoba et al. (2019) suggest that at least some ESA astronauts can be expected to not respond as well to in-flight training as the individual reported by Hides et al. (2016). The other studies used for comparison also have very low participant numbers. Chang et al. (2016) and Bailey et al. (2018)

both have n = 6, which severely impacts our ability to compare programmes and make valid and useful conclusions. Future research, which includes measuring pre-flight, immediately post-flight and post-reconditioning LM CSA for all long-duration mission ESA astronauts, would be beneficial to confirm the countermeasure/ reconditioning programme is effective.

Harrison et al. (2018) collected in-flight ultrasound imaging data, as well as pre- and post-flight MRI data. They found that disc height and disc angle appeared to follow a phased pattern, increasing early in-flight before decreasing later in-flight. An early phase of adaptation, up to FD90, was characterised by IVD hyperhydration swelling. The swelling resolved by around FD150, at which point muscle atrophy was the prevailing spinal change. Six reported back and neck pain in the group of seven astronauts early in-flight, and three needed further medical investigation and intervention post-flight, including a microdiscectomy. The early increase in IVD height, which resolved later in the flight, may explain the lack of IVD height changes seen by Bailey et al. (2018) and Chang et al., (2016) post-flight and explain the IVD changes seen during bed rest. Spinal changes seen in bed rest will be discussed further in section 2.3.2

2.3.2 Spinal changes seen in bed rest

Human spaceflight research is expensive and often limited by operational constraints (Green & Scott, 2018; Ploutz-Snyder, 2016). As a result, ground-based simulations are used to simulate aspects of the spaceflight environment, supplementing, and complementing spaceflight research by allowing a more detailed study of physiological changes (Cromwell et al., 2018), with more control and potentially larger participant numbers (Poltz-Snyder 2016). Green and Scott (2018) provided a succinct and comprehensive review of the current ground-based simulations used by ESA, which include head-down tilt bed rest (HDT), dry immersion and hyper-buoyant floatation (HBF). Head-down tilt bed rest is favoured by ESA because it is well-tolerated by participants compared to dry immersion, while HBF is still a very new spaceflight simulation model with few studies available (Green & Scott, 2018). As such, this review will focus on head-down tilt bed rest.

To date, there have been almost 100 papers published using the bed rest model. Studies have been undertaken by all major space agencies, ranging in duration from five to 120 days. Although one study used exclusively female participants, many studies have used only male participants, and more recent studies have included male and female participants. The effects of a wide range of interventions, such as exercise, lower body negative pressure, nutritional supplementation, artificial gravity, and testosterone supplementation, have been studied on muscle, bone and cardiovascular outcomes. However, it is not clear how many studies have been completed or which papers report on the same studies in some instances due to study naming conventions. A summary of these data are given in Appendix D (from Laws et al., unpublished data).

Four long duration (56-90 days) studies were identified from the wider bed rest study pool from the spinal health. OneNASA 90-day supine study with 29 participants looked at low-magnitude vibration as an intervention (Holguin et al., 2009). Two studies were of 60-day duration, including the Second Berlin Bed Rest Study (BBR-2) (Belavý et al., 2010; Belavý et al., 2017; Hides et al., 2011) and WISE-2015 (Holt et al., 2016). The Berlin Bed rest study (BBR2) involved 24 male participants undergoing HDT and split into resistive exercise, resistive exercise and whole-body vibration or control groups. The WISE 2005 study (Holt et al., 2016) involved 16 female participants undertaking either treadmill running in Lower body negative pressure (LBNP), flywheel exercise, and a non-exercising control. Finally, The Berlin Bed Rest Study 1 (BBR1) (Belavý et al., 2012; Belavý et al., 2008) utilised horizontal bed rest for 56 days with twenty male participants divided into a control and resistive exercise countermeasure group.

There are also two shorter duration 28-day twins studies identified: one with 15 pairs of identical twins (seven female and eight male sets) utilising treadmill running in lower-body negative pressure (LBNP) (Macias et al., 2017), and one 12 pairs of twins (seven female and five male sets) (Cao et al., 2005). A summary of studies discussed in this section is shown in table 2.2.

Table 2-3 Summary of the bed rest papers discussed in this section.

Study	Paper	Bed rest posture	Study duration in days	Intervention	Participant number
NASA 90 day study with low back pain	Holguin et al. 2009	supine	90	Low-magnitude vibration	18 male, 11 female
Berlin Bed rest Study 2 (BBR2)	Belavy et al. 2010, and 2017	HDT	60	Resistive exercise or resistive exercise and vibration	24 male
WISE 2015	Holt et al. 2016	HDT	60	Treadmill or flywheel in LBNP	16 female
Berlin Bed rest Study (BBR)	Belavy et al. 2008 and 2012	supine	56	Resistive exercise	20 male
NASA Twins 28 day Study	Macias et al. 2007	HDT	28	Twins, LBNP treadmill running	16 male and 14 female
NASA 28 day Twins Study	Cao et al. 2005	HDT	28	Twins, LBNP treadmill running	Ten male and 14 female
Berlin Bed rest Study 2 (BBR2)	Hides et al. 2011	HDT	60	Resistive exercise or resistive exercise and vibration	24 male

Overall, there is consensus that spinal offloading leads to muscle atrophy of the lumbopelvic muscles during bed rest. The extent of the atrophy depends on the length of the study, the intervention type, the level and muscle or muscle groups studied. In the longest study by Holguin et al. (2009) used CT scans from T-12 to L3 to monitor the paraspinal muscle cross-sectional area. They found that cross-sectional area decreased 7.3% in the control group and 6.6% in the intervention group, with an incidence of low back pain being associated with greater levels of muscles atrophy (Holguin et al., 2009).

Belavy et al. (2010 and 2017) (BBR2) found that spinal muscle atrophy could be detected within 48-hours of the start of bed rest. However, caution must be taken when interpreting these findings as the volumetric loss may be attributed to cephalic fluid redistribution rather than actual physiological, structural changes (Berg et al., 1993). By the end of the bed rest period, Transversus Abdominis (TrA) had reduced by 18% in the non-exercising controls, but only by 4-5% in the exercise groups, suggesting that resistive exercise or resistive exercise with whole-body vibration are at least partially successful at mitigating TrA muscle atrophy. No studies were identified which quantified how much lumbopelvic muscle atrophy is detrimental and how much, if any, is trivial; therefore, it is not known if 4-5% change is clinically meaningful or not. Future research which identifies a clinically meaningful change in TrA size would be beneficial.

Using ultrasound imaging during BBR2, Belavy et al. (2010 and 2017) found that, on average, between L1 and L5, LM CSA decreased by around 4% in both the exercise and control groups, but with as much as 6-7% at the L5 level, suggesting that the intervention was not successful at preventing LM muscle atrophy despite axial loading being applied to the spine via the exercise device harness. In an earlier paper reporting the outcomes of BBR2, Belavy et al. (2010) reported that similar to spaceflight; the participants experienced more LBP and higher visual analogue scores for pain in the first week of HDT with pain peaking on HDT2, suggesting that the participants may also have experienced a period of early adaptation similar to that seen in SABP.

In another BBR2 paper, (Hides et al., 2011) looked at the impact of a post-bed rest exercise intervention using either specific motor control exercise or general strengthening with trunk flexion for five consecutive days after the bed rest period on lumbopelvic muscle cross-sectional area at each level between L1 and L5. From recovery day 2 (R+2) to R+7, participants undertook exercise for 30 minutes, followed by two supervised sessions and a home exercise program between R+8 and R+14, and seven follow up supervised sessions between R+16 and R+89. MRI was taken pre-bed rest on R+14 and R+90. Both training programs were successful at restoring LM CSA as measured, and the flexion exercise program was able to increase the CSA to greater than the pre-bed rest levels at L1 and L3 (Hides et al., 2011). Interestingly, the conclusion was that specific motor control exercises were better than general exercises because of lower compressive forces in the spine, despite both types of exercise being effective and similar pain reports. However, (Hides et al., 2011) did not report on the home exercise program adherence, so it is unknown if the programs were followed as prescribed and whether spinal forces did differ in the groups following discharge from the bed rest facility. Therefore, it is not possible to determine which exercise type was more beneficial

The WISE 2005 study had comparable HDT methodology and results to BBR-2. The intervention was partially successful in preventing paraspinal muscle atrophy in women at the L3/L4 level, with a reduction of 4.3±3.4% in the exercise group compared to 10.9±3.4% in the control group (Holt et al., 2016). However, all paraspinal muscles were measured as a group, and Erector Spinae (ES) contributed to nearly 80% of this reduction. When considering LM alone, both groups experienced a significant decrease, suggesting that the LBNP treadmill running and flywheel exercise intervention were ineffective at preserving LM specifically, and the authors suggested that the paraspinal muscles should be assessed individually (Holt et al., 2016).

WISE 2005 participants completed pain questionnaires throughout the study and found that exercise helped reduce the number of consecutive days when pain was experienced. However, due to different reporting techniques, it is not possible to compare the results with the BBR-2 to see if there were common LBP patterns in bed rest participants between both studies. Non-standardised reporting and data collection techniques were the major limitations identified in a recent systematic review of bed rest studies, which limits does not allow for meta-analysis and data pooling, reducing the overall usefulness of bed rest data (Winnard, Nasser, et al., 2017b). Winnard, Nasser, et al. (2017b) suggested that future bed rest studies aim for consistency in outcome reporting to minimise this issue.

During BBR1, Belavý et al. (2008) found that resistive exercise with vibration reduced LM atrophy at the L4 level compared to the control group. They also found that LM and ES atrophy increased throughout the bed rest duration, while Rectus Abdominis and Psoas hypertrophied, probably due to the flexed position participants adopted while in bed. Lumbar Multifidus and ES partially recovered during the 180-day follow up period, with trunk flexors also returning to near-baseline values. A reduction in lumbar lordosis angle was seen in both groups, with the authors showing a weak correlation between increased disc height, lordosis angle and LM CSA.

Belavý et al. (2012) showed with surface electromyography (sEMG) that the superficial paraspinal muscles, including Lumbar and Thoracic Erector Spinae (LES and TES, respectively), Internal Obliques (IO) and External Obliques (EO), increased flexor/extensor co-contraction in the control group, while the exercise intervention ameliorated this. However, the significance of the changes seen in this study is hard to assess as the authors do not clearly state them, and the hypothesis being tested is unclear. A possible interpretation of the results suggests that not only does exercise countermeasures help to reduce paraspinal muscle atrophy. It also helps to maintain normal patterns of movement and muscle recruitment.

BBR-1 utilised horizontal bed rest (Belavý et al., 2012; Belavý et al., 2008), with participants being allowed to be up to 30° head-up during waking hours. This bed position was a major limitation of this study, negating both the cephalic fluid shift and +0Gz gravity vector. Spinal loading was a by-product of the resistive exercise hardware design, much like on the ISS. The participants were loaded via an over-shoulder harness to 1.2-1.8 times body weight (BW) for 5-10 minutes twice per day. This is significantly higher than loading achieved on the ISS (Belavý et al., 2012).

Spinal changes were also seen in short duration bed rest studies, showing that deleterious spinal changes happen in a relatively short amount of time following unloading. Macias et al. (2017) found that global spinal extensor strength, measured on a lumbar extensor dynamometer, decreased after 28 days of bed rest in the non-exercising controls, while the exercise group saw reductions between 0-24° flexion, but only minimal changes at higher angles. The greatest spinal extensor weakness was seen in an upright posture. This finding is interesting because it suggests that there may be a range of motion in which the spine is at particular risk of injury, which would support the spinal stability hypothesis posited by Bergmark (1989), Panjabi (1992) and (Hoffman & Gabel, 2013). In contrast to Belavý et al. (2008), bed rest-induced lumbar lordosis flattening was not seen in 28-day HDT (Macias et al., (2017), suggesting spinal morphological changes have a temporal element or that some countermeasures are more successful than others at maintaining normal spinal posture.

Cao et al. (2005) also looked at twin pairs during 28-days of HDT, with each pair containing a control and exercising twin. The exercising twin undertook daily treadmill training in lower-body-negative pressure. This study found that the cross-sectional area of Erector Spinae at the L3-4 level decreased 7.7 ± 1.3% in the control group and 6.8 ± 0.7% in the exercise group, both showed a significant decrease, and there was no significant difference between the control and intervention groups. Psoas was also measured and showed no significant changes in this study (Cao et al., 2005).

One of the limitations of the current pool of bed rest studies that report on LBP is that they have mostly been conducted by one research team, leading to the possibility of bias, both in the reporting of results and hypothesis testing. Two long-duration studies, BBR1 and BBR2, representing 48 participants, have multiple papers, with at least two papers seemingly reporting the same data (Belavy et al., 2010; Belavy et al., 2017), potentially artificially inflating the bed rest LBP data pool. Additionally, it is not always clear in the wider bed rest literature which bed rest study each paper refers to or how papers are linked, although a systematic review is underway to try and clarify this (Laws et al., unpublished data). In the future, it would be beneficial if all bed rest study research used study names to identify commonalities between different papers.

Further bed rest research is needed to clarify what spinal changes occur as part of the unique physiological demands placed on the body by the bed rest platform, for example, related to +Gx loading, skin pressure changes and cervical spine/upper body position, especially where the current research disagrees, for example flattening of the lumbar lordosis (Belavý et al., 2008; Macias et al., 2017). Only one study looked at the reconditioning programme after bed rest specifically. It showed no preference or additional benefit from either motor control training or trunk flexion and general strategy exercises, although the authors argue that motor control training benefits beyond muscle hypertrophy (Hides et al., 2011). Therefore, future research should look at which interventions are most effective at lumbopelvic muscle rehabilitation after deconditioning to aid both terrestrial LBP patients and post-flight astronauts.

As with the spaceflight exercise countermeasures discussed in section 2.1, no bed rest intervention has successfully prevented the deterioration of the spine and lumbopelvic muscles during bed rest, although some interventions partially successfully reduced at least one aspect of deconditioning. Because no effective lumbopelvic 'in-flight' countermeasure has been identified, post-flight reconditioning is required. The following section will look at what is known about post-flight reconditioning.

2.4 Post-flight Reconditioning

One of the main aims of post-flight reconditioning is to return the astronaut to their pre-mission function as quickly and effectively as possible to reduce injury risk (Febus, 2020b). As with in-flight countermeasures, NASA, ESA and RSA approach post-flight reconditioning in a variety of ways. Cosmonauts have attended a post-flight sanatorium/health retreat; however, no data about what this involved were found in English (Stupin et al., 1991). American, Canadian and Japanese astronauts all undertake the NASA reconditioning programme, while European astronaut follows the ESA reconditioning pathway (Loehr et al., 2015). As well as the general shared aim of returning astronauts to their pre-flight function (Loehr et al., 2015), the ESA program has the additional objectives of restoring postural muscle control using the principles of Motor Control Training, in which correct postural alignment supersedes and precedes strength training (Lambrecht et al., 2017). Table 2.3 summarises the ESA and NASA reconditioning programmes (Lambrecht et al., 2017; Loehr et al., 2015; Petersen et al., 2016). A difference between NASA and ESA reconditioning programmes appears to be the involvement of the ESA physiotherapist in the initial stages (Hides et al., 2021; Lambrecht et al., 2017). One interpretation is that ESA approaches reconditioning similar to an athlete returning from injury (Dhillon et al., 2017) with the assistance of healthcare and exercise professionals (Hides et al., 2021; Lambrecht et al., 2017) and NASA approaches reconditioning like a pre-season training campaign (Argus et al., 2010) under the guidance of strength and conditioning professionals (Loehr et al., 2015). Hides et al. (2016) found, in an N = 1 astronaut study, three weeks of supervised motor control training, strength training and postural control training exercises in water and the gym. Pre-post flight LM CSA at L5 reduced 9.98cm^2 to 6.99 cm^2 before returning to pre-flight levels by R+14. However, this research needs to be considered carefully as it represents the experiences of only one astronaut and may not be transferable to the wider astronaut population. Newer research suggests that spinal deconditioning following spaceflight persists for at least 12 months (Johnson et al. 2010), and potentially as long as four years (Burkhart et al. 2018) following a 6-month flight; therefore, future research needs to focus on spinal reconditioning to reduce the risk of ongoing spinal health issues.

Table 2-4 A brief overview of ESA and NASA post-flight reconditioning

	ESA[a]	NASA[b]
Duration	21 days	45 days
time/ day	2hr	2hr
Aim of the program	To return to pre-flight baseline, reduce risk of injury, restore postural control, utilise MC approach to normalise neuromuscular control and ensure motor control is normal before strengthening exercises	To return to prefight baseline promptly
Team	Space Medicine Team: multidisciplinary team including physiotherapists and exercise scientists	Strength and conditioning, and rehabilitation team
Structure of the program	Acute R+0 - R+21: physio and exercise Phase 2 R+22 - R+45: independent program	R+0 - R45
Resistance exercise	From R+5, on set days in the pathway	every other day- same exercises as in-flight
Aerobic Exercise	from R+2: cycling, rowing, partial loading treadmill and circuit training	every day progressed as vestibular symptoms allow: recumbent cycle, upright cycle, treadmill, outside running
Other skill areas	stretching, plyometrics, jumping drills, kettlebells, martial arts, gym ball	agility, medicine ball, cone drills, static and dynamic stretching, jumping drills, balance drills; different skills are introduced at different time points during recovery
other	R+0 - R+21: 1-hour physio and 1 hour of guided exercise; R+1 - R+7: pool-based exercises	R+0-Dynamic stretching and warm-up, mobility, balance and proprioception, medicine ball and static stretching R+1- core exercises R+7-Ladder and cone drills R+21- jumping drills*

a Lambrecht et al. 2017, (Lambrecht et al., 2017; Loehr et al., 2015; Petersen et al., 2016) b: Loehr et al., (2016), Scheuring (2017)

2.5 Conclusion

2.5.1 Inflight Exercise Countermeasures

Current in-flight exercise countermeasures only have limited data available to demonstrate their effectiveness in maintaining lumbopelvic muscle health. However, cross-sectional muscle area (Bailey et al. 2018) and spinal length and disc changes (Harrison et al. 2018), combined with reduced function (Mulavara et al., 2018), changes were seen post-flight suggests that the USOS current countermeasure program is minimally effective at best. Although the ESA case study is promising Hides et al. (2016), this lacks generalisability as an n = 1 study. Only minimal data are available about post-flight reconditioning for either actual or simulated spaceflight; therefore, further research is needed into post-flight reconditioning and how it can be optimised for future long-duration LEO and planetary missions. When considering in-flight countermeasures, space agencies approach exercise prescription differently. Recent terrestrial reviews aimed at improving in-flight countermeasures (Jones et al., 2019 and Steele et al., 2019) suggested that all programme designs need to be reconsidered to optimise the training opportunities on ISS. Researchers also need to be aware that inter-agency differences within a crew may impact the physiological changes seen in microgravity research.

2.5.2 Bed Rest Countermeasures

Spinal deconditioning has been studied during and after bedrest ranging between 28- and 90-days duration. During the Berlin bedrest study, two and the WISE 2005 campaigns exercise countermeasures were able to partially mitigate losses in lumbopelvic muscle cross-sectional area, however individual muscles responded differently to the exercise intervention, and Lumbar Multifidus appear to be particularly susceptible to atrophy the lower lumbar area (Belavý et al., 2010; Belavý et al., 2017; Holt et al., 2016). However, in the 28-day twin study, Cao et al. (2005)

found no difference in Erector Spinae and Psoas cross-sectional area between the exercise in Lower Body Negative Pressure and no-exercise control. It is not clear from the data currently available whether exercise countermeasures designed to ameliorate muscle loss in the lower limb effectively target the lumbopelvic muscles. Only one paper was identified which considered the post-bedrest reconditioning period(Hides et al., 2011). This study compared two exercise modalities and found similar recovery levels in the lumbopelvic muscle cross-sectional area results after 90 days. However, this study relied on a home exercise program with intermittent follow-up after the first seven days of recovery; therefore, although the authors suggested that motor control training was beneficial and trunk flexion and general exercise, caution must be taken because the true level of activity and exercise type was not closely monitored the study. More research is needed to understand the recovery time course of the lumbopelvic muscles following long-duration bed rest and determine if there is an additional benefit from following a specific spinal exercise program compared to whole-body reconditioning to further our understanding spinal reconditioning following offloading.

2.5.3 Post-flight reconditioning

As with offloading following bed rest, post-flight reconditioning of the lumbopelvic muscles has been little studied to date. Only one case study was identified, which looked at astronaut lumbopelvic reconditioning following a long-duration space mission (Hides et al., 2016). The study found that this astronaut Lumbar Multifidus cross-sectional area returned to pre-flight levels after 14 days of reconditioning, including spinal specific motor control training (Hides et al., 2016). However, other research suggests that spinal deconditioning and increased spinal injury risk may be present between one (Johnston et al., 2010) and four years (Burkhart et al., 2019). Therefore, more research is needed to determine what happens to the spine following offloading to improve computer modelling operational exercise provisions in-flight and determine the optimal reconditioning period.

The following chapter details the shared methologies for the Low Back Pain and AGBRESA bed rest studies, which combined will add to the understanding of how spines behave in a deconditioned state and how targeted reconditioning using the Functional Re-adaptive Exercise Device may help improve lumbopelvic reconditioning.

3 Chapter 3 General Methodology

This thesis consists of two Functional Re-adaptive Exercise Device (FRED) intervention studies. The first study, referred to as the Low Back Pain (LBP) study, consisted of 14 participants undertaking six weeks of FRED exercise for up to 15 minutes three times per week. The participants were working-age adults, mostly recruited from the staff at Northumbria University, who experienced chronic non-specific low back pain, which responded to mechanical load. The second study formed part of the large scale, multinational ESA/NASA 60-day head down Artificial Gravity Bed Rest Study (AGBRESA) and consisted of 13 days of FRED exercise for up to 30 minutes during the reconditioning phase of the study. In the AGBRESA study, 24 healthy working-age adults were randomly assigned to either continuous artificial gravity (AG) on a short arm human centrifuge, intermittent AG, or no-AG controls during the Head Down Tilt (HDT) period; the intervention groups were then assigned either standard reconditioning, or standard reconditioning supplemented by FRED reconditioning, in balanced groups.

These studies were used to help create a ground-based understanding of how FRED exercise might be beneficial for post-flight reconditioning in astronauts. Some data collection methods were shared between both studies, and these are discussed below alongside the study-specific methodologies.

3.1 Low Back Pain Study

The Low Back Pain Study's planned methodology is given below, while alterations, deviations, and adaptations to the study design are discussed in their respective findings chapter.

3.1.1 Participants

Fourteen participants (seven female, seven male) were recruited to take part in the study. One female participant left the study after the initial recruitment phase due to a change in work commitments and was removed from all data analysis. The remaining 13 participants had a mean age of 46±9 years, a mean height of 1.73±0.84m and a mean mass of 75±12 kg (BMI 24.8±3) at the first data collection. The mean mass was reduced by 1±3kg by the end of the intervention period.

3.1.2 Recruitment and Screening

An email was sent to all staff and postgraduate researchers at Northumbria University, which was subsequently forwarded to non-University members. This email identified 81 interested parties, who were then provided with further information about the study and asked to return the Physical Activity Readiness Questionnaire (PAR-Q) and the Fear Avoidance Beliefs Questionnaire (FABQ). Twenty-five individuals returned both screening questions. Individuals were considered for further screening if the PAR-Q suggested FRED activity would be safe for the individual and the FABQ score was <15 (Williamson, 2006). Some individuals chose to self-exclude from further consideration to join the study at this point, with fear of needles and high BMI being the most common reasons provided. In total, 19 people were invited to the physiotherapy screening, which took place in August 2016 by the Senior Physiotherapist (DD). Individuals were considered for inclusion if they had:

- A numeric rating scale for pain (NRS) >4 (participants were not informed of this requirement to limit bias)
- Pain or discomfort that was increased by physical activity
- Symptoms of pain that originated between L1 and S5 and were not referred from another area.
- No red or yellow flags that would contraindicate FRED exercise (Kenyon & Kenyon, 2009)

- BMI was <28, or if over 28, the adipose tissue was carried away from the abdomen, allowing for intramuscular EMG electrode placement (not covered in this thesis).
- Symptom duration was longer than eight weeks.
- Could commit for the duration of the study, including having no holidays booked at the start of the study.
- In the view of the Senior Physiotherapist, treatment was clinically indicated,
- Demonstrated that they could safely mount, dismount, and use FRED.

Following the physiotherapy assessment, two people were excluded due to a high BMI with excessive abdominal adipose tissue, two people were unable to meet the time commitment to the study, and one person failed to attend their appointment. Figure 3.1 shows a flow diagram of the recruitment process with reasons for exclusion.

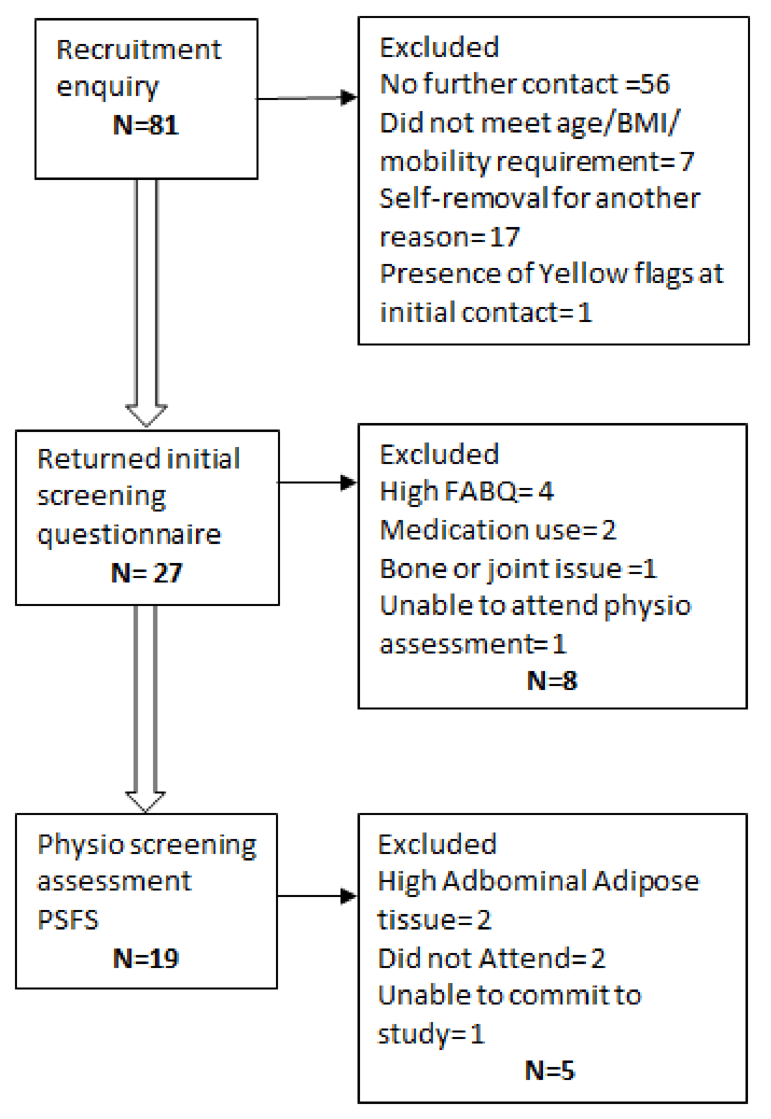


Figure 3-1 Recruitment and selection process for the LBP study

3.1.3 Training intervention

3.1.3.1 The FRED device

Previous research about FRED and the device particulars is covered in detail in chapter one, section 1.4. Briefly, FRED is a modified cross-trainer that has nearly friction-free footplates mounted on the flywheel. The rear of the footplate arm can be adjusted to make the ellipse of the footplate path longer and steeper, increasing the exercise challenge (Winnard et al., 2016). FRED provides a postural challenge in an upright standing position and has been shown to activate the deep lumbopelvic muscles (Caplan et al., 2014; Debuse et al., 2013; Gibbon et al., 2013; Weber et al., 2017; Winnard et al., 2016; Winnard et al., 2017a, Winnard et al., 2017)

3.1.3.2 The LBP FRED intervention

The FRED exercise intervention lasted six weeks, with three 15-minute training sessions per week. The exercise was progressed in duration and difficultly according to participant ability, fatiguability and pain symptoms. The planned training pathway is shown in table 1.1. The training program and any deviations or adaptations needed during the study are discussed in more detail in chapter 4.2.1. Full details of how participants used FRED and data acquisition related to FRED are included in section 3.4.3.

Table 3-1 FRED training protocol

Exercise pattern	Total rest time (minutes)	Total exercise time (minutes)
1x 6 min (first session only) 3x 2min	2	6
4 x 2 min	3	8
5 x 2 min	4	10
6x 2 min	5	12
4x 3 min	3	12
5x 3 min	4	15
Increase crank to the next level	2	6

3.2 Outcomes specific to the Low Back Pain Study

The Low Back Pain study collected a wide range of outcome measures, including static balance parameters, ultrasound imaging of the Transverus Abdominis (TrA) and Lumbar Multifidus (LM) muscles, FRED movement variability, questionnaires and daily activity logs. Although 3D motion analysis and electromyography data were collected, they are outside the scope of this thesis and will not be considered further. Each participant attended the Gait Laboratory at Northumbria University on four occasions for data collection, in addition to screening and training visits. The first visit (A1) took place six weeks before the start of the FRED intervention. The second visit (A2) was in the week before the start of the FRED intervention. They attended in the week following the FRED intervention (A3) and six weeks after the end of the FRED intervention (A4). Fifteen weeks after the end of the FRED intervention, each participant was sent the questionnaires to complete (A5).

Table 3-2 Data collection undertaken during each laboratory session in the LBP study.

	A1: BDC1 6 weeks before FRED	**A2: BDC2 immediately before FRED**	**A3: Immediately post FRED**	**A4: 6 weeks post FRED**	**A5: 15 weeks post FRED**
USI	✓	✓	✓	✓	
Balance	✓	✓	✓	✓	
FRED exercise	✓	✓	✓	✓	
Motion capture*	✓	✓	✓	✓	
EMG*		✓	✓		
Questionnaires	✓	✓	✓	✓	✓

* Data not covered in this thesis.

The following sections provide an overview of outcomes specific to the Low Back Pain study, including Patient-Specific Function Scale (PSFS), SF-36, and self-reported activity levels and medication use. Other measures, including abdominal ultrasound imaging, balance, and FRED exercise, also used in the AGBRESA Bedrest Study, are presented in section 3.4.

3.2.1 Lumbar Multifidus USI

Lumbar Multifidus USI was collected in the prone position on a plinth with a face hole, with the arms relaxed down by the side. Paper towel was tucked into the waistband of the shorts/ trousers of each participant to prevent the gel from spoiling clothing. LM thickness at the L5 level was taken with the transducer in a longitudinal position. LM cross-sectional area (CSA) was collected with the transducer in a transverse position at the L5 level (Hides et al., 2016), confirmed by laminar topography. Participants were asked to lift the ipsilateral leg just off the examination couch with a straight leg lift to activate the LM and aid in muscle boundary identification. If the LM was slow to respond or the boundary was unclear, the contralateral leg was also moved. The lateral border of LM was marked on screen, and where necessary extra images were taken with the entire muscle border marked, using the boundary tool on the USI machine. Video of left and right LM was recorded to aid later data analysis. LM USI was only used for the LBP study.

3.2.2 Patient-Specific Functional Scale (PSFS)

The Patient-Specific Functional Scale (PSFS) is a patient-reported questionnaire in which participants self-identify Activities of Daily Living (ADL) which are impacted by their physical impairment (Stratford, 1995), in this case, low back pain. Zero represents a task that is impossible to complete, and 10 represents no impairment with the task being completed normally. Therefore, on the PSFS, higher scores represent a better function. The MCID for aggregate scores is two (Sterling, 2007)

For the LBP study, participants were asked to identify only tasks limited by their LBP, which they would score as a zero at the start of the study; this was to limit potential ceiling effects from successful treatment. Importantly in this group of community-dwelling adults, each task was constrained by a time and pain level, so a zero-score presented a specific circumstance in which the participant could not complete the task, rather than total physical impairment. An example PSFS ADL task might be "unable to stand washing dishes for 10 minutes pain-free" or "driving to work for 30 minutes with an increase in pain of less than 4/10".

Each participant completed the PSFS at every data collection (A1-A5). Because of the diverse nature of the PSFS tasks selected, both in task-type, duration and pain intensity, PSFS results were only grouped by task-type to allow for analysis (e.g., standing tasks, sitting tasks, bending, twisting or lifting tasks, physical activity tasks). Standing activities included tasks such as washing dishes or standing on a whiteboard. Sitting tasks included desk work, driving and seated hobbies. Bending, twisting, and lifting tasks included putting on socks, lifting loads or employment tasks requiring repeated twisting movement. Physical activities included all other activities which lead to an increased heart rate, such as sport, dog walking and other energetic hobbies or employment activities. A task could be included in more than one group, the predominant movement-type causing the limitation for grouping. An example of this is donning socks; this was a popular activity to report on the PSFS, and while typically undertaken in sitting, it was the bending aspect that leads to a functional limitation; therefore, it was classed as a bending activity.

3.2.3 SF-36 (UK short recall)

The SF-36 is a standardised, validated, general health/wellbeing questionnaire scored between 0-100, with higher scores representing better function and wellbeing (Jenkinson et al., 1999). It is a holistic approach to measuring health-related outcomes rather than LBP specific. SF-36 can be used to monitor both physical and mental health domains (Jenkinson et al., 1999). The SF-36 was administered on paper at each data collection time point and then analysed using the UK normative data provided by the Health Outcomes Scoring Software version 5.0 (QualityMetric, Rhode Island, 2017).

3.2.4 Self-reported activity levels and medication use

An Excel Online survey was used to administer a personalised eight-question log, of which five questions required answers, although three of these had default answers to reduce the participant workload. The questions are shown in Appendix B. All participants had the same questions in the same order, but activities and medication type were personalised. Each participant was reminded weekly to complete their log, and once per experiment segment (e.g., baseline period), a list of absent days was emailed to the participants to fill in missing data.

Activities were grouped by perceived exertion level into very light, light, moderate and vigorous levels. Very light activities included indoor household chores such as washing dishes or vacuuming; light activities included a slight increase in heart rate but still able to comfortably hold a conversation, for example, walking the dog. Moderate activities left the participant slightly out of breath, such as jogging or cycling, and vigorous activity resulted in breathlessness and a raised heart rate, such as running and competitive sport. Heart rate was not formally assessed in this study, but each participant was asked to rate how much exertion was needed to complete their ADL. Because of this, some activities were included in different categories for different participants. For example, jogging may have been classed as moderate for one participant and vigorous for another.

3.3 The Artificial Gravity Bed Rest Study (AGBRESA) Study.

The NASA/ESA Artificial Gravity Bed Rest Study (AGBRESA) was a 60-day 6° head-down tilt long-duration bed rest study conducted at :envihab in Cologne, Germany. It aimed to assess the efficacy of artificial gravity by centrifugation and multisystem (i.e. cardiovascular, musculoskeletal and vestibular) countermeasures. The AGBREA study consisted of The International Standard Measures, four NASA-selected experiments and seven ESA-selected experiments (Ngo-Anh., 2017). Hence, the FRED study was part of a large cohort of measures taken, which required methodological compromises to achieve the best balance of science for all research teams.

3.3.1 Participants

Twenty-four participants (eight female and 16 male) were selected after completing a series of medical, psychological, and physiological tests carried out by the Institute of Aerospace Medicine at the German Aerospace Centre (DLR). Participants had an average age of 33±9 years, 1.75±0.9m tall and 74±10kg in mass. The participants were split into two cohorts. Cohort 1 (C1) completed their involvement in the study between March and July 2019. Cohort 2 (C2) completed their involvement in the study between September and December 2019. All participants originally assigned to C1 completed the study. Eight of the participants assigned to C2 completed the study successfully. However, four of the C2 participants were withdrawn on medical grounds before they started or completed the baseline data collection. These four participants were replaced by four new participants who then completed the study successfully three weeks behind the original C2 schedule.

3.3.2 Study Design

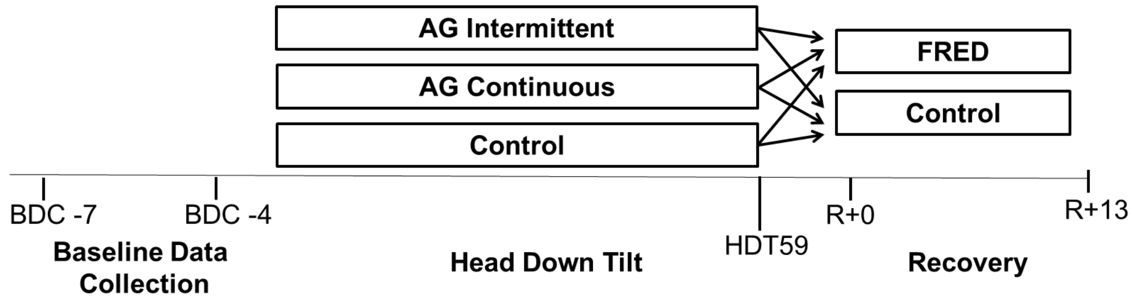
3.3.2.1 Bed rest routines

From 0900 on head-down tilt day, 1 (HDT1) participants were required to be in the 6° HDT position at all times. They were not permitted to use pillows to prevent interference with the cephalic fluid shift (Laurie et al., 2019). Participants could move in bed, but one shoulder had to be in contact with the bed at all times, and excessive movement was discouraged and monitored via video throughout the study (Kramer et al., 2020). The participants day ran from 0600 to 2200, with all activities of daily living and experiments carried out in the HDT position. Environmental factors were controlled for all participants with a room temperature of 22.5 °C (C1 = 22.7 ± 1.6 °C; C2 = 22.5 ± 1.6 °C) (Attias et al., 2020), water intake 50ml/kg body mass/day and energy intake 1.6 base metabolic rate in BDC and recovery, and 1.3 base metabolic rate in HDT (Kramer et al., 2020).

3.3.2.2 Group assignment

Participants were pseudo-randomly assigned to either 30 minutes of continuous (cAG) or five times six minutes of intermittent Artificial Gravity (iAG) countermeasure or no countermeasure Control (Ctrl) groups during HDT by study staff at DLR. centrification was approximately 1G at the calculated centre of mass (Kramer et al., 2020). Participants were then balanced assigned from each countermeasure group into either FRED-exercise or no-exercise control group during the recovery phase in a counterbalanced way, as shown in Figure 3.2. During the second campaign, one participant from the supplementary group was assigned to the FRED exercise but was reassigned to the control group for logistical reasons before starting the recovery data collection. A balance between the AG groups was maintained when the participant was reassigned.

Figure 3-2 AGRESA study design. BDC- baseline data collection, HDT: head down tilt, R: recovery. BDC and HDT phases were timed from the first day of HDT, so BDC-4 is in the baseline phase, four days before bed rest, while HDT7 is one week into bed rest. The recovery phase time started from the first days of re-ambulation, or R+0.



3.3.3 Outcomes specific to the AGBRESA Study

The following section provides an overview of outcomes specific to the AGBRESA study, including pain questionnaire and MRI. Other measures, including abdominal ultrasound imaging, balance, and FRED exercise, also used in the Low Back Pain Study, are presented in section 3.4.

On BDC-7, participants received a 30-minute protocol familiarisation session, which included FRED familiarisation training with coaching. USI was collected on BDC-4, HDT59 and R+13. Balance and FRED data were collected on BDC-4, R+0 and R+13. Data collection time points are shown in figure 3.2, and details of the data collected at each time point are given in table 3.3.

Table 3-3 Data collected during each session in the ABGRESA study

	BDC-4 (4 days before HDT)	R+0 (immediately post-HDT)	R+13 (14 days post HDT)
USI[a]	✓		✓
Static balance	✓	✓	✓
FRED	✓	✓	✓
EMG /Rapid Arm Movement	✓	✓	✓
MRI[c]	✓		✓
Pain questionnaire		✓	

[a] Due to time constraints on R+0, USI data were collected on HDT59

[b] Data not covered in this thesis

[c] MRI data were also collected on HDT60

[d] Pain Questionnaires were given in the evening on BDC-12 and BDC-1, HDT1-7, then every 7-days in HDT, R+0 to R+7 and R+12

3.3.3.1 MRI

MRI data were collected using a 3 Tesla Magnetom Vision system (Siemens, Erlangen, Germany), with participants in the HDT supine position. Two sets of 64 transverse scans taken from the T12 vertebra to sacrum (T1 weighted DIXON-VIPE sequence, total acquisition time = 5 minutes; slice thickness = 4 mm; distance factor = 20%, TR = 7.02 ms, TE1 = 2.46 ms, TE2 = 3.69 ms, flip angle = 5 deg; field of view = 400 mm x 400 mm at 1.0 mm x 1.0 mm pixel size). Multifidus at L5/S1 muscle cross-sectional area was measured using OsiriX DICOM viewer for Mac (v.10.0.5, Pixmeo SARL, Bernex, Switzerland), and data extraction was carried out by one person (EDM).

3.3.3.2 Low Back Pain Questionnaire

Pain Questionnaires were given during BDC (BDC-12 and BDC-1), weekly during HDT (HDT7, HDT14 etc.), each day during the first week of the recovery phase (R+1 to R+7) and on the penultimate recovery day (R+12). Questionnaires were provided in German and were administered by the AGBRESA study nursing team in the evening at around 2130. The questionnaire was developed in collaboration with a research team from Charitè University, Berlin. The questionnaire is shown in Appendix C.

3.3.4 Post-bed rest reconditioning

3.3.4.1 Standard reconditioning

The AGBRESA study compared the effects of either standard reconditioning or standard reconditioning plus FRED exercise. Standard rehabilitation was a generic exercise intervention delivered by physiotherapists for one hour on days R+4 to R+11, with a rest day on R+8 (Lee 2020, private communication). Exercises were based on postural control and movement co-ordination and stretching. Strength training was against body weight (Lee 2020, private communication). Exercises included activities like ladder drills, catching and throwing, body-weight push-ups, squats, and calf raises; an example of the equipment used is shown in figure 3.3. The specific routines and exercises were not recorded, so information such as exact exercise prescribed, repetitions, sets, body area focus etc., cannot be assessed.

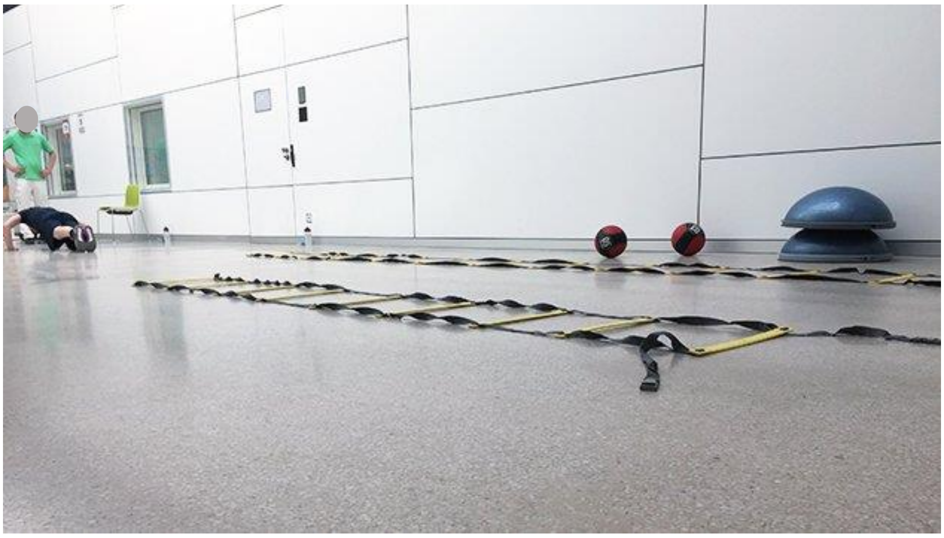


Figure 3-3 shows an example of the training equipment used in the standard reconditioning.

3.3.4.2 FRED intervention

Participants The Low Back Pain Study results informed the design of the AGBRESA FRED intervention protocol. Total exercise time in the LBP study was 177 ±12 minutes. Therefore, the AGBRESA protocol was designed to build up over four sessions (R+1 to R+4), followed by 15 minutes of training between R+5 and R+13. The total training time of 178 minutes to provide a comparable total training load within the 13-day timescale. All AGRESA testing and training was undertaken using the crank 5 (0.20m), without progression to larger cranks because most participants in the LBP study only progressed after 13 training sessions. The planned training pathway is shown in table 3.4.

Table 3-4 Planned AGBRESA training protocol with exercise times and rest times

Study Day	Exercise pattern	Total rest time (minutes)	Total exercise time (minutes)
R+1	3 x 2 min	4	6
R+2	5 x 2 min	2	10
R+4	4x 3 min	3	12
R+5 to R+13	5x 3 min	4	15

3.4 Outcomes common to the Low Back Pain Study and AGBRESA Study

Some data collection techniques were common across both studies, and these key outcomes are discussed in the following subsections. Key Outcomes included lumbopelvic muscle imaging, patient-reported pain, balance tasks, FRED exercise and data acquisition. Due to logistical constraints and data sharing, there were some differences in how key outcomes were collected, as shown in Table 3.2.

Table 3-5 Key outcome differences between the LBP and AGBRESA studies.

TrA= Transverus Abdominus, LM= Lumbar Multifidus, USI= Ultrasound imaging, MRI= magnet Resonance Imagaing, NRS= Numeric Rating Scale for Pain, FRED= Functional Re-adaptive Exercise Device.

Area	Outcome	LBP Study	AGBRESA Study
Imaging	TrA USI	✓	✓
	LM USI	✓	
	LM MRI		✓
Pain	VAS		✓
	NRS	✓	
	Pain map		✓
Balance	Static Balance	✓	✓
FRED	FRED Dynamic balance and control	✓	✓

3.4.1 TrA Imaging

Magnetic Resonance Imaging (MRI) was used to measure the Lumbar Multifidus (LM) cross-sectional area (CSA) in the AGBRESA study. Because MRI was not available in the LBP study, Ultrasound Imaging (USI) was used instead. The Transversus Abdominis (TrA) thickness was measured by ultrasound in both studies, as the MRI T1 weighted Dixon Sequence produced artefact due to respiration in the anterior abdominal area.

In the LBP study, TrA USI was collected with the participants in a horizontal supine position with a pillow under the head and a double thickness pillow under the knees for comfort. Hands and arms rested at the side of the body in a neutral position, and a paper towel was used to protect the participants' clothing. Images were taken at end-expiration during normal tidal breathing (Teyhen et al., 2005). The transducer was positioned transversely halfway between the illiac crest and lower rib, which coincided with most participants' level of the umbilicus. The transducer was positioned so that the tip of TrA and the thoracolumbar facia was visible roughly in the middle section of the image, with sufficient lateral shift to maintain the tip onscreen once the muscle contracted. The transducer was angled slightly diagonally down towards the pubis to better imagine the hyperechoic facial lines where required. For the contracted TrA images, participants were first advised to "pull your belly button towards the spine as hard as you possibly could in a 100% contraction" as they exhaled to facilitate the abdominal drawing-in manoeuvre (ADIM). In the LBP study, the first ADIM was not recorded but used to gauge how much the muscles would move for later images, with the transducer being repositioned as necessary to ensure TrA would remain visible throughout the 30%MVC contractions. Participants were coached in how to activate the TrA on exhalation using three different descriptions:

1. Imagining a string with ten knots going through the belly button, which would produce a 100% contraction if all the knots were pulled through the belly button.
2. Imagining being relaxed as 0% and having the belly button pulled towards the spine as hard as possible as 100% (often used after the participants were able to activate the TrA with little feedback)
3. Imagining zipping up a tight pair of jeans which required bringing the belly button to come in and up, where the top of the zip represented a 100% contraction.

4. To account for language differences in the AGBRESA study, the USI instruction was altered to ‘pull your belly button towards the bed as hard as you can, making yourself thin’ because the original instructions produced an abdominal crunch rather than an ADIM.

Active contraction images were recorded with TrA at 30% MVC. Regardless of the visualisation technique used, all participants were reminded to try and achieve a 30% contraction on exhalation each time. In the AGBRESA study, it was decided to record the 100% MVC contractions as well, so these were recorded first with a pause (2-3 breaths) before the 30% MVC images.

For the AGBRESA study, participant positioning was slightly altered from that described above to comply with the HDT protocol. Therefore, no pillow was placed under the participants head to avoid possible confounding factors with a caudad fluid shift in other studies, and all images were taken in the HDT position. The transducer’s position was also altered to account for the head-down position and resulting cephalic shift of the abdominal contents. The transducer was positioned approximately mid-way between the lower rib and umbilicus, which is higher than the standard position. The starting position was found by placing the left index finger in line with the umbilicus and the middle finger on the lowest rib, with the transducers placed in the finger spacing, with additional small movements of the transducer to optimise the image on the screen. The transducer was tilted to compensate for the participant body angle. This ensured that the transducers were vertical to the long axis of the body rather than the floor.

In the LPB study, images were captured with an Esaote Tecnos MP T7500 (Italy) ultrasound machine with a 5-7 MHz curvilinear transducer, set to 7 MHz for all images. The transducer was used in conjunction with Aquasonic 100 Ultrasound

Transmission gel (Parker Laboratories Inc, Fairfield USA). Each image was captured using an Epiphan DV12USB3 frame grabber (Epiphan Systems Inc, Canada) and 64bit Windows 8/8.1driver, version 3.3 (Epiphan Systems Inc, Canada) to a Lenovo computer for storage and later analysis. The frame grabber was required due to the near-obsolete CD-write save function on the ultrasound machine. Each muscle was imaged three times on the left and right side of the body. If there was any doubt about image quality, more images were taken.

In the AGBRESA study, images were collected using a GE LOGIQ e BT 12 portable ultrasound (General Electric Healthcare, USA) using a 5MHz curvilinear C4 transducer. Images were collected at resting end-expiration, at approximately 30% MVC and 100% MVC. Images were collected at BDC-4, HDT60 and R+13. The images were coded with a random 4-digit alphanumeric code, generated by RANDOM.org. Participant identity and timepoint were blinded at the point of data extraction. Images were saved in the DICOM format and transferred to a MacBook Pro (Apple, California, USA) for later analysis with OsiriX software (v.10.0.5, Pixmeo SARL, Bernex, Switzerland).

3.4.2 Balance Task

Participants completed a range of balance conditions, with each successive condition increasing the challenge to postural stability (Table 3-3). Each condition lasted 70 seconds, or until the participant experienced a loss of balance (such as stumbling, using arms coming up more than approximately 30°), whichever came sooner. The balance task in both studies was undertaken on an AMTI OR6-7 force platform (Watertown, MA, USA) force platform.

Table 3-6 Oder of balance tasks

Balance tasks undertaken on the force platform balance task	Visual Input
Bilateral	Eyes Open
Bilateral	Eyes Closed
Single-leg-stand (R)	Eyes Open
Single-leg-stand (R)	Eyes Closed
Bilateral Block (LBP only)	Eyes Open
Bilateral Block (LBP only)	Eyes Closed
Bilateral AIREX balance pad (AGBRESA only)	Eyes Open
Bilateral AIREX balance pad (AGBRESA only)	Eyes closed

In the LBP study, participants stood on a 9cm wooden block, using the protocol detailed in Mok et al., (2004). In The AGBRESA study, this was changed to an Airex foam balance pad (Sins, Switzerland) due to the potentially increased fall/injury risk and foot pain (T. Miokovic et al., 2014) immediately post-bedrest

During the LBP study, the force platform was mounted in the laboratory floor. To standardise the starting position for the balance task, participants had their neutral foot position marked on individual sheets of non-slip fabric, which were then placed on markers on the force plate. Data were collected into the Vicon Nexus (Vicon Motion Systems Ltd UK), with power supplied AMTI MSA-6 amplifier (Watertown, MA, USA). This provided an excitation voltage of 10V and amplified the signals at a nominal gain of 4000hz before they were sampled via a Vicon MX unit (Vicon Motion Systems Ltd UK) and stored within Nexus for analysis. The signals were then exported as text files before being imported into Matlab (The Mathworks Inc, Natick, Massachusetts). for processing using custom-written scripts (The Mathworks Inc, Natick, Massachusetts). Due to an error during data collection at A2, two-three participants recorded a left single-leg stand. Both left and right single-leg stands were performed to account for this deviation at the A3 data collection.

The AGBRESA study was undertaken at the ;envihab facility in Cologne, Germany; therefore, a bespoke mounting platform was constructed from Rexroth (Bosch, Schwieberdingen, Germany) aluminium sections with a plywood floor and non-slip surface. Data were collected from the force plate via an AMTI MSA-6 amplifier (Watertown, MA, USA) and the cDAQ-9174 CompactDAQ with NI9201 Analogue input module, which also collected the FRED frequency and footplate top dead centre data. Data were sampled in a custom LabView 2018 program (National Instruments, Hungary) to where the data were stored in a matrix for post-collection analysis using custom Matlab (The Mathworks Inc, Natick, Massachusetts) code. The force plate was covered with a double thickness of non-slip, non-compressible flooring (1.56mm) to keep the top surface flush with the mounting frame. Participants were asked to stand with their feet facing squarely forward hip-distance apart in the bilateral conditions and to stand approximately in the middle of the force plate during the single-leg standing condition. The single leg-stand task was only recorded for the right leg due to time constraints.

3.4.3 FRED Variability Task

In the LBP study, FRED frequency and footplate top dead centre data were fed into LabChart 8.1.46 (AD Instruments Australia) via an ML138 BioAmp and 16/30 PowerLab (AD Instruments, Australia, instead of LabView and CompactDAQ used in the AGBRESA study and discussed above

The FRED data collection task itself comprised of a three-minute familiarisation session) (Winnard et al., 2017a) followed by a one-minute data collection with FRED set at the smallest crank size of 0.2m, or crank setting 5, with participants able to stop after the familiarisation period if they felt fatigued. If able, the data collection followed directly from the familiarisation. Participants were told when the data collection time started. Previous research by (Winnard et al., 2016) defined the optimal FRED velocity as $0.42ms^{-1}$ at the 0.2m crank setting, which can be derived from the raw rotary encoder data, via pulse a period calculation to define the time taken for the footplates to move 1/1000th of a revolution, the actual frequency can then be derived by the following equation where f = frequency, T = time in seconds.

;

$$f = (\frac{1}{T})/100$$

Equation 1 Actual FRED frequency calculation

Participant feedback was presented as a target frequency± range, which was scaled to the Strouhal number of 0.2 (Winnard, Debuse, et al., 2017), calculated by;

$$f = \frac{st.v}{A}$$

Equation 2 Target frequency calculation

Where f = target frequency, st = Strouhal number of 0.2, v = velocity of $0.42ms^{-1}$ and A = crank radius of 0.2m, therefore at the smallest crank setting, the target frequency was 0.42Hz ±0.2Hz.

In the LBP study the target frequency was also calculated for each crank setting, which are shown in table 3.6

Table 3-7 scaled target frequency for each crank setting, starting at the smallest (5) to the biggest (1)

Crank Number	Crank position radius (m)	Target frequency (Hz)	± Range (Hz)
5	0.20	0.42	0.20
4	0.28	0.30	0.143
3	0.36	0.233	0.111
2	0.425	0.198	0.09
1	0.50	0.168	0.08

Participants received feedback on a screen in real-time at eye level when standing on FRED. In the LBP study, the feedback trace was provided at a rate of 50:1 as a smoothed output using a triangle Bartlett filter. Participants were instructed to keep the trace within the target area, which appeared white, while the out of bounds areas appeared red. In the AGBRESA study, FRED frequency was calculated using the LabView counter function to determine the pulse period to calculate the output frequency, which was displayed as a real-time graph with a 100hz low pass filter. The moving trace was white on a black background, without of bounds areas coloured blue.

In the initial familiarisation period, individualised coaching was provided to ensure a proper FRED technique. Examples of FRED coaching points included;

- Ensuring participants had slightly bent knees during the exercise
- Encouraging participants to shift their weight back to the foot's heel to allow for improved control on the downward stroke of the cycle.
- Reminding participants to breathe while holding their abdominal muscles slightly engaged in maintaining the correct hip and spinal posture.
- Reminding participants to relax their arms and hands and avoid bracing postures.

3.4.4 Patient-Reported Outcome Measures (PROMS)

In the LBP study, the Numeric Rating Scale for Pain (NRS) was used to record participant pain. It is an 11-point (0-10) scale in which zero represents no pain and 10 represents the worst pain. Participants select a number value between 0-10 for their pain symptoms in the last 24 hours. The minimal clinically important difference is 2 points (Salaffi et al., 2004).

The AGBRESA study used the Visual Analogue Scale (VAS), which is similar to the NRS but uses a 10cm line with end anchors of ‘no pain’ on the left-hand side and ‘worse pain’ on the right-hand side instead of whole numbers. Participants mark the line to show their average pain in the last 24 hours, and higher numbers represent more intense pain symptoms. An MCID of 1.1-1.37cm have been suggested (Hawker et al., 2011)

The NRS and VAS are very strongly correlated and are not likely to be influenced by other factors, such as emotional state (Thong et al., 2018). The NRS was chosen for the LBP study because of the ease of use and transferring data for analysis. The VAS was chosen for use in AGBRESA in conjunction with a collaborating team from the Charitè University as part of a longer pain questionnaire, shown in Appendix B.

4 Chapter 4 Patient-Reported Outcome Measures in the Low Back Pain study

4.1 Introduction.

As outlined in chapter one, FRED was developed as a potential reconditioning tool for paraspinal muscle deconditioning following spaceflight. However, initial testing of FRED on an astronaut population was not possible due to the limited number of spaceflights each year. Therefore, chronic non-specific low back pain patients were used as an alternative model population (Stokes et al., 2016). The following three chapters will discuss the influence of 6-weeks of FRED exercise in a cohort of community-living people with chronic non-specific low back pain (LBP). To gain a patient-centred, holistic overview on the effects of FRED exercise, this chapter will look at Patient-Reported Outcome Measures (PROMS) for pain intensity, patient-reported function and self-reported analgesic use, activity levels and general mental and physical health.

4.2 Methodology

The LBP study was undertaken at Northumbria University in the autumn of 2016/spring 2017. Fourteen participants were recruited to participate in the LBP study to undertake up to 15 minutes of FRED exercise three times per week for six weeks. One participant left the study after the initial data collection due to a change in work commitments. Full details of the participant recruitment and screening process were provided in section 3.3.1.

4.2.1 Training intervention

Participants attended the Gait Lab at Northumbria University three times per week. One session included ultrasound imaging (USI) and exercise, and two sessions comprised of exercise alone. Due to work and other, commitments some participants (FR2016GT07, FR2016DM04 and FR2016TW05) experienced at least one time-compressed session, in which two exercise sessions worth of FRED time was delivered in one day, with a 15-minute break between sessions. One participant (FR2016HL01) moved permanently on to the compressed timetable of one USI/ exercise and one double exercise session every week from Week 2 as a change in work commitments meant they could not attend the third session on a separate day.

Initially, it was envisioned that participants would train in one continuous block, and pilot testing was carried out with three people performing up to 29 minutes of exercise to see if this was feasible. While 29 minutes in one block was repetitive and participants lost focus, it was physically possible in younger, healthy participants. However, during data collection with the older clinical patients, one participant noted that six continuous minutes in the first session did not feel like an appropriate training time compared to the length of travel to the University and may struggle with more extended periods due to fatigue. Therefore, an interval programme was introduced to ensure each participant received sufficient rest time between blocks to avoid muscle fatigue that might impact the quality of the exercise while also ensuring participants felt they got “value for money” out of their training time, especially for those who travelled into the University specifically to take part in the study. The training protocol is shown in Table 4.1.

Table 4-1 Ideal FRED training progression

Exercise pattern	Total rest time (minutes)	Total exercise time (minutes)
1x 6 min (first session only) 3x 2min	2	6
4 x 2 min	3	8
5 x 2 min	4	10
6x 2 min	5	12
4x 3 min	3	12
5x 3 min	4	15
Increase crank to the next level	2	6

Participants were progressed in time after each session if they were symptom-free at the current level and were held when needed, for example, due to leg pain and fatigue. One participant (FR2016KM14) could not complete 2-minute training blocks for the first three weeks; therefore, they exercised in blocks of 90 seconds until their fitness levels allowed them to exercise for a longer duration. Participants progressed to a harder crank setting if their movement variability showed a 30% improvement (Ostelo et al., 2008) or better when compared to the Assessment 1 (A1) baseline movement variability, and they could complete 15 minutes of exercise with no adverse effects or symptoms. FRED technique was assessed by looking at the movement variability, or standard deviation, from the mean frequency over one minute using the calculation functions in LabChart 8.1.46 (AD Instruments Australia). When asked to rate their performance, participants were able (from week 3 onwards) to self-identify a ‘good’ section and a ‘poor’ section with a change in movement variability of 0.01Hz. By the end of the intervention period, two participants (FR2016NN11 and FR2016DW13) could discriminate between even smaller variations.

Participants were always supervised by KL while in the lab as part of the standard lab protocol. All participants were coached to improve their FRED performance, with no participant needing coaching after week 2. Some exercise sessions were held jointly between two participants, depending on scheduling requirements. Over the intervention period, participants undertook a total of 177±12 minutes of FRED exercise.

4.2.2 Patient-Reported Outcome Measures

Briefly, PROMs included paper questionnaires for the Numeric Rating Scale for Pain (NRS), a 0-10 scale which measures pain intensity (Hawker et al., 2011), the Patient-Specific Functional Scale (PSFS), which measures changes in the performance of self-selected activities of daily living (Sterling, 2007). The Patient-Specific Functional Scale is scored between 0-10, with higher numbers representing better function. The minimum clinically important difference (MCID) for aggregate scores is 3 (Stratford, 1995), although an MCID of 2 in LBP patients was suggested following a systematic review (Horn et al., 2012). The SF-36 is a holistic well-being questionnaire covering both mental (MCS) and physical health PCS). It is scored between 0-100, with higher scores representing better health (Jenkinson et al., 1999). In addition to the standard analysis, the SF-36 was analysed using the Health Outcomes Scoring Software Version 5 (2017), which allows for a comparison of results between the study sample and national normative values (Saris-Baglama et al., 2010). Questionnaires were administered on paper at the start of each data collection appointment.

One researcher (KL) verbally conducted the NRS and PSFS to ensure consistency. At the A1 baseline data collection session, assessment questionnaires were available electronically and in hard copy; however, due to the low take-up (3/14) of the electronic questionnaires, they were administered in paper format only for all other assessments. All questionnaire data were transferred to Microsoft Excel 360 (Microsoft, USA) for analysis. Daily online logs were kept for the duration of the study about activity levels and analgesic use. Eleven participants completed 85.5% of the requested logs, representing 1891 participant days. Two participants were excluded from the daily logs data analysis because they kept logs weekly despite prompting (FR16GT07 and FR16DW13). The log questions are shown in appendix A.

4.2.3 Statistical analysis

Statistical analyses were carried out using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). All data were treated as non-parametric after failing a Shapiro-Wilks test. A Freidman test was carried out, followed by a post hoc Wilcoxon Ranked Sign Test if significance was indicated. A $p = 0.05$ was used for significance. Cohen's d ~~e~~ffect sizes were calculated using Microsoft Excel 2016 with thresholds for size as Cohen (1988) defined.

Comparisons were made between BDC (A1), pre-intervention (A2), immediately post-intervention (A3), six-week follow-up (A4), and 15-week follow up, which was email only (A5) for the PSFS, NRS and SF-36. Activity levels and Analgesic use were divided into three six-week blocks of baseline (BDC), intervention (INT) and post-intervention (POST).

4.3 Results

4.3.1 Patient-Specific Functional Scale (PSFS)

The Friedman's test showed a significant change in function between pre and post-intervention $\chi^2 F(3) = 3.476$, $p = 0.001$. Following the FRED intervention, all participants showed improvement in their chosen activities of daily living higher than the MCID, which was maintained at follow-up, as shown in Figures 4-1 to 4-4. There was a slight increase in scores during the baseline period; however, this was less than the MCID.

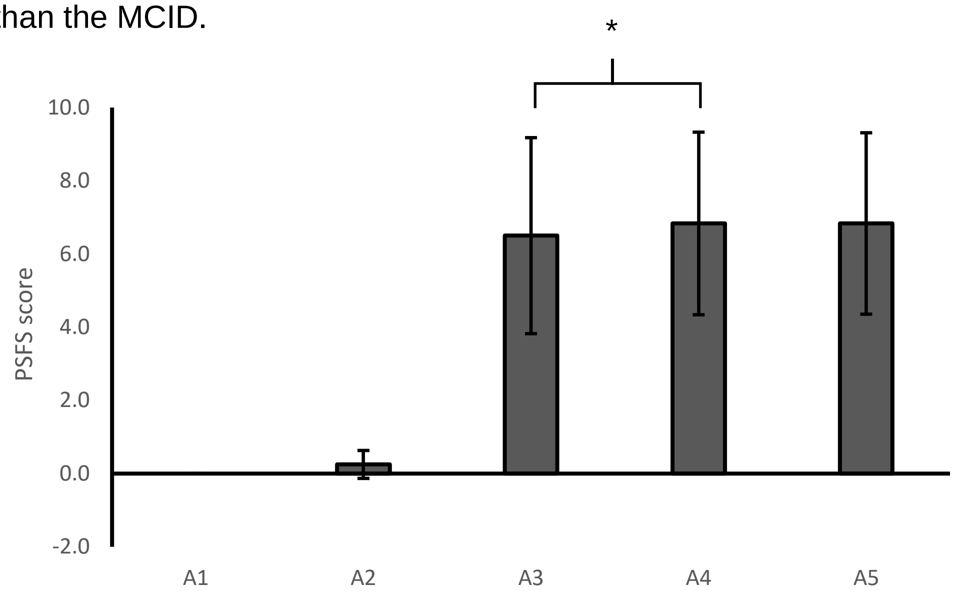


Figure 4-1 presents the mean (+/-) standard deviation scores for the Patient-Specific Functional Scale for standing-related activities at each measurement point (A1-A5). * Indicates a change from baseline (A1) greater than the minimal clinically important change of 2.

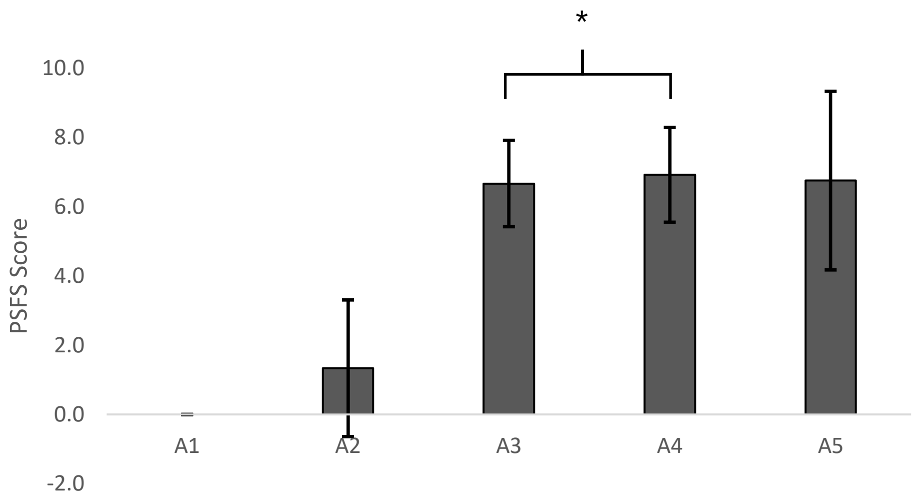


Figure 4-2 presents the mean (+/-) standard deviation scores for the Patient-Specific Functional Scale for sitting-related activities at each measurement point (A1-A5). * Indicates a change from baseline (A1) that is greater than the minimal clinically important difference.

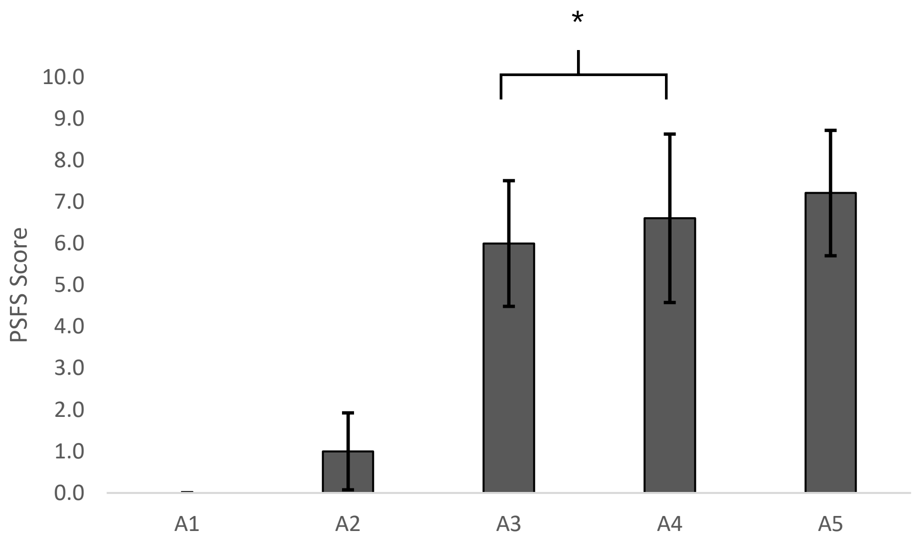


Figure 4-3 Figure 4.3 presents the mean (+/-) standard deviation scores for the Patient-Specific Functional Scale for bending, lifting and twisting-related activities at each measurement point (A1-A5). * Indicates a change from baseline (A1) that is greater than the minimal clinically important difference.

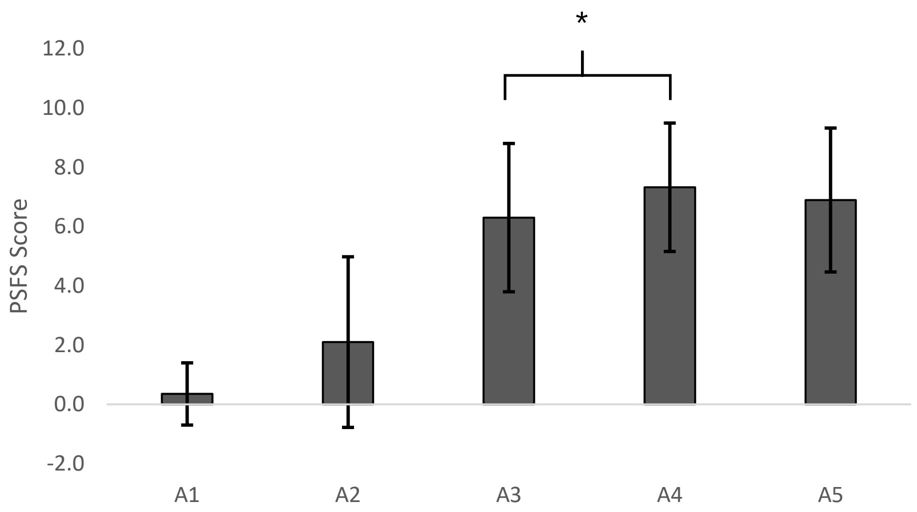


Figure 4-4 presents the mean (+/-) standard deviation scores for the Patient-Specific Functional Scale for physically demanding activities at each measurement point (A1-A5). * Indicates a change from baseline (A1) that is greater than the minimal clinically important difference

Table 4-2 PSFS results. Bold indicates significant difference at the level p<0.05

Variable	Comparison	Δ Mean	Confidence Interval (95%)				
			Upper	Lower	effect size	Z	Sig.
Standing Activities	A2 – A1	0.25	0.08	0.30	1.31	-1.34	0.18
	A3 – A2	6.25	0.66	2.39	4.09	-2.20	**0.03**
	A4 – A2	6.58	0.62	2.25	4.58	-2.20	**0.03**
	A5 – A2	6.58	0.62	2.24	4.60	-1.30	0.19
	A4 – A3	0.33	1.12	4.05	0.13	-2.21	**0.03**
	A5 – A4	0.00	1.08	3.89	0.00	-0.37	0.71
Sitting Activities	A2 – A1	1.33	0.43	1.54	1.35	-1.34	0.18
	A3 – A2	5.33	0.70	2.52	3.31	-2.21	**0.03**
	A4 – A2	5.58	0.72	2.61	3.34	-2.21	**0.03**
	A5 – A2	5.42	0.99	3.56	2.38	-2.21	**0.03**
	A4 – A3	0.25	0.57	2.05	0.19	-0.54	0.59
	A5 – A4	-0.17	0.86	3.09	-0.08	-0.32	0.75
Bending Activities	A2 – A1	1.00	0.22	0.71	2.16	-1.89	**0.06**
	A3 – A2	5.00	0.58	1.86	4.10	-2.38	**0.02**
	A4 – A2	5.61	0.70	2.25	3.80	-2.37	**0.02**
	A5 – A2	6.21	0.58	1.85	5.11	-2.37	**0.02**
	A4 – A3	0.61	0.84	2.70	0.34	-0.85	0.40
	A5 – A4	0.61	0.84	2.69	0.34	-0.32	0.75
Physical Activities	A2 – A1	1.75	1.10	2.83	0.89	-2.03	**0.04**
	A3 - A2	4.20	1.51	3.87	1.56	-2.81	**0.01**
	A4 - A2	5.22	1.39	3.66	2.07	-2.67	**0.01**
	A5 - A2	4.79	1.46	3.85	1.81	-2.68	**0.01**
	A4 - A3	1.02	1.28	3.38	0.44	-2.00	**0.05**
	A5 - A4	-0.43	1.24	3.36	-0.19	-0.68	0.50

4.3.2 The Numeric Rating Scale for Pain (NRS)

The Friedman's test showed no significant change in the NRS scores pre-post intervention $\chi^2F(3) = 5.075$, p = 0.1.66. The NRS score changes pre-and post-intervention were less than the MICD. There was considerable individual variation in pain pre- and immediately post-intervention, where six participants (46%) experienced at least a 2-point reduction in pain at the A3 timepoint. Four participants had no change in pain, and three participants experienced a 1–5-point increase in pain immediately post-intervention. One participant (FR2016FM) reported a complete resolution of symptoms and was pain-free at the end of the study.

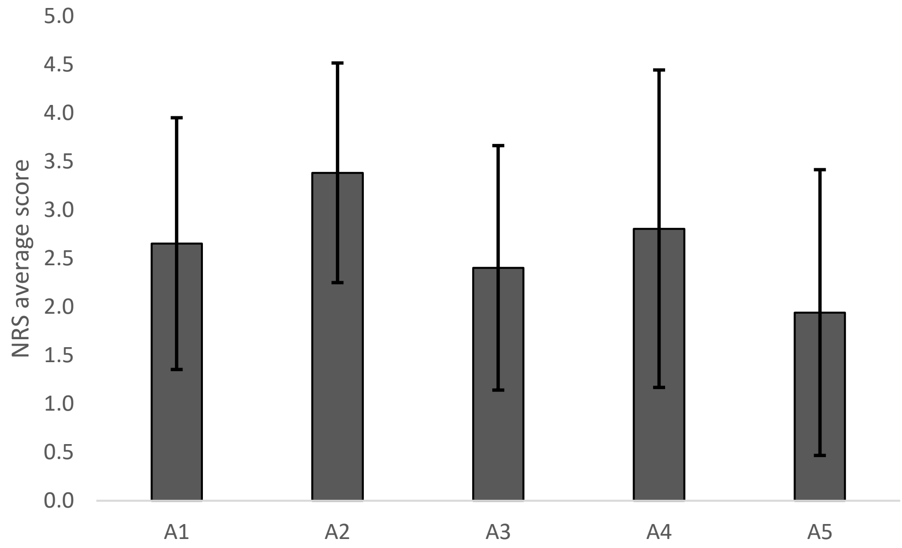


Figure 4-5 NRS average scores± standard deviation. There were no changes greater than the MCID, and the Friedman test showed no significant changes pre-post intervention.

4.3.3 Short Form 36 UK short recall (SF-36)

A Friedman's test showed no significant change in either mental or physical component scores between pre and post-intervention, with a physical component score of $\chi^2F(1) = 0.692$, $p = 0.405$ and a mental component score of $\chi^2F(1) = 0.077$, $p = 0.782$. Physical health appears to have increased slightly between A2 and A3, which remained higher than baseline in the post-intervention follow-up period, shown in figure 4.6. However, the mental health component score appears to have reduced slightly at the end of the study, shown in figure 4.7.

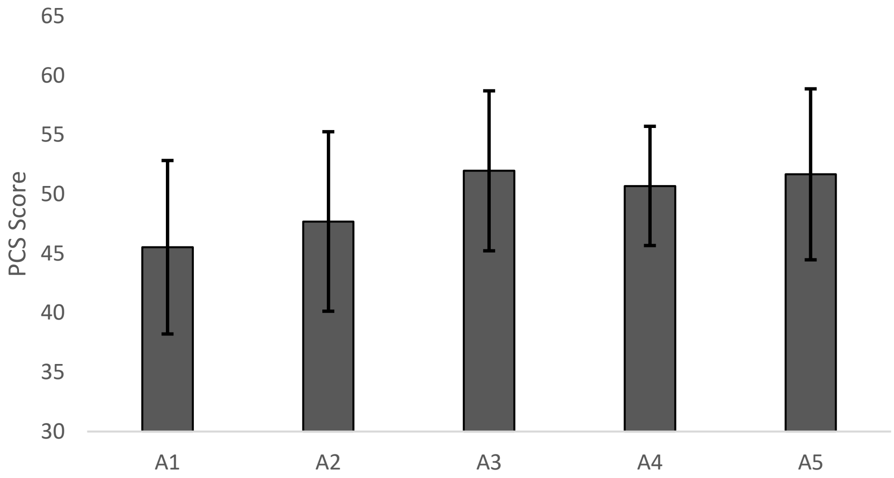


Figure 4-6 shows the SF-36 physical mean scores ±SD. Although there was no significant change pre-post intervention, there was a slight increase post-intervention, which was maintained for the rest of the study.

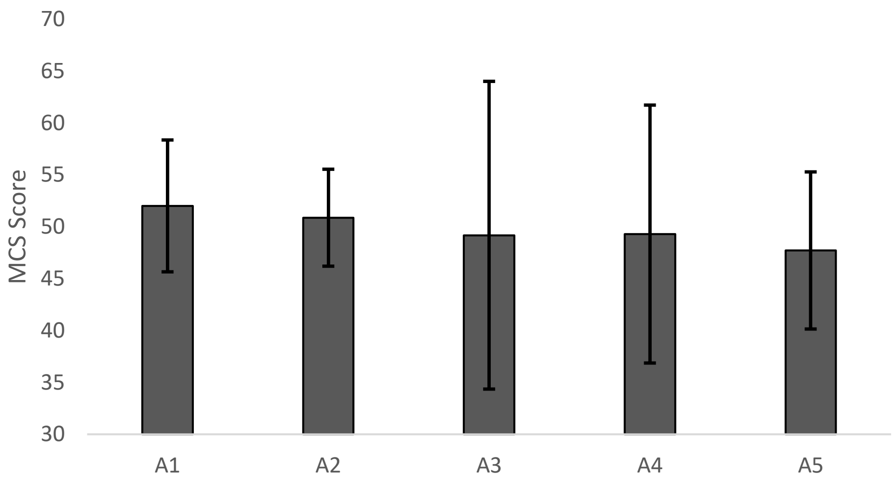


Figure 4-7 shows the SF-36 component mean scores ±SD. Although there was no significant change pre-post intervention, there was a slight increase post-intervention, which was maintained for the rest of the study.

Compared to the UK national average scores, more participants were above the national average PCS after undertaking FRED exercise than before, with a 7% change representing one person changing category, shown in figure 4.8. In contrast, figure 4.9 shows the population comparison for the MCS.

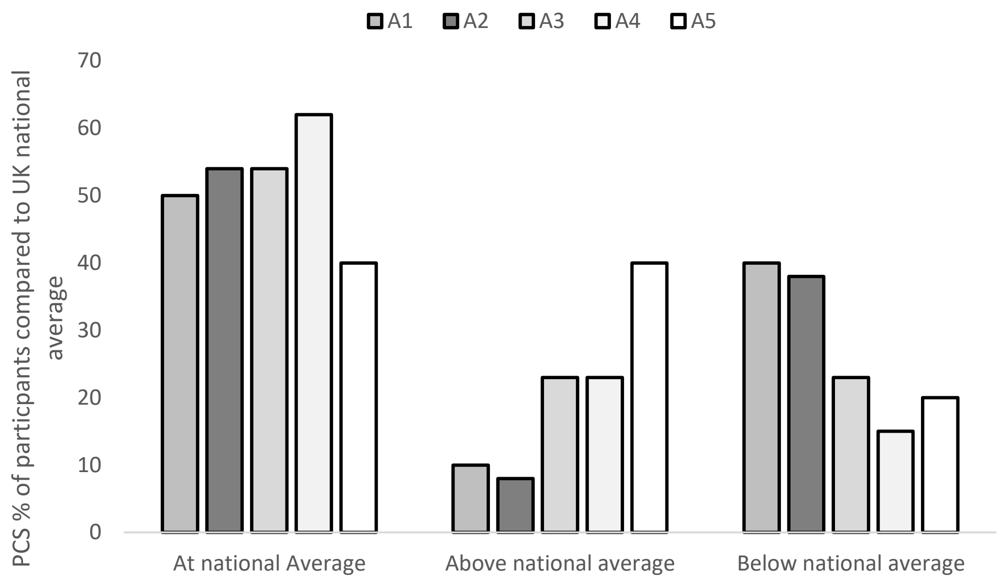


Figure 4-8 shows the percentage of participants who were at, above or below the UK national average score in the physical domain

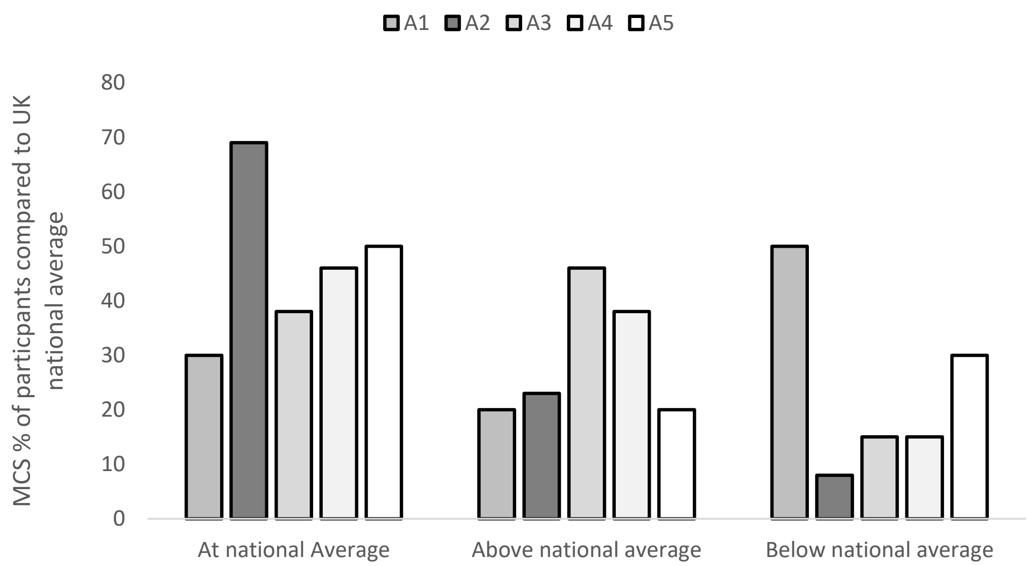


Figure 4-9 shows the percentage of participants who were at, above or below the UK national average score in the mental health domain

4.3.4 Self-Reported activity and analgesic use.

There were no significant changes in activity level between BDC, INT and POST, at any activity level, with Friendmen's results of $\chi 2F(2) = 1.00$, $p = 0/607$ for very light activity, χ2F(2) = 4.33, p = 0.115 for light activity, χ2F(2) = 1.33, p = 0.513 for moderate activity and χ2F(2) = 4.33, p = 0.115 for vigorous activity levels. Activity levels tended to drop throughout the experiment, especially the more vigorous outdoor activities, shown in figure 4.10.

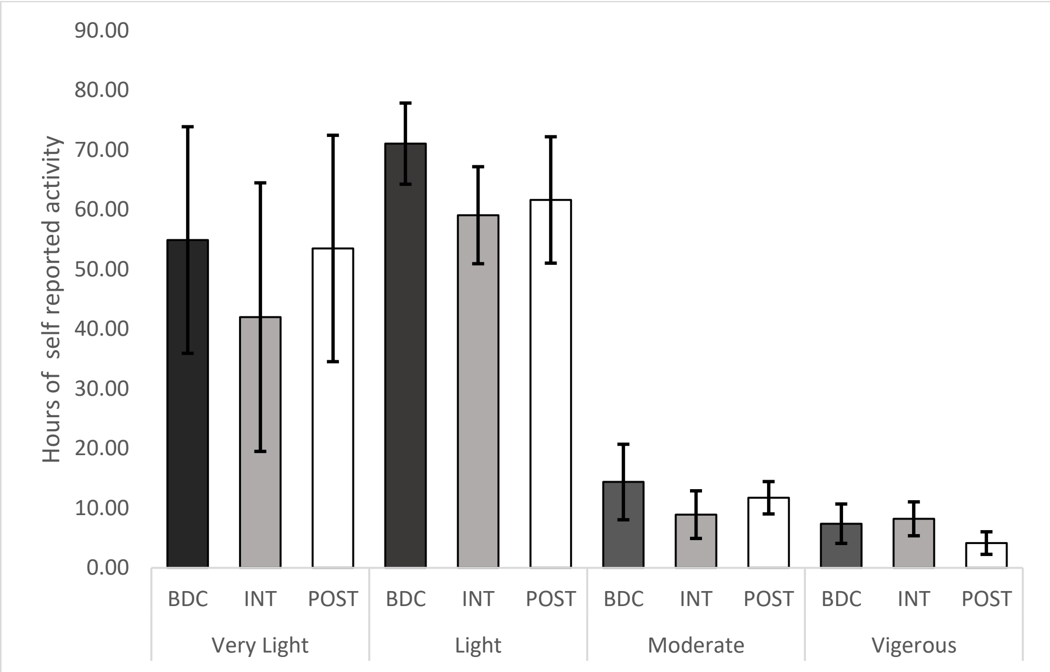


Figure 4-10 shows the self-reported activity levels during each 6-week measurement period. There was no significant change throughout the study.

4.3.5 Analgesic use

Statistic testing was not carried out on analgesic use due to the skewed nature of the data analgesic use was low throughout the study, with 256 participant-days (12.7%) with analgesic use. However, 134 participant-days (51.9%) with analgesic use represented just one participant (FR2016KM14). The next highest reported medication user (FR2016SL12) reported 40 days (15.5%). All participants analgesic use is shown in table 4.3. One participant (FR2016DM04) reduced their normal medication dose by 50%. Two reported episodes of increased LBP did not require analgesics (FR2016PJ03, FR2016HL01).

Table 4-3 All participants self-reported Analgesic use and their percentage of the study total, showing Analgesic use was heavily skewed towards participant 14.

Participant	**Total number of days with analgesic use**	**% of the total**
14	134	51.3
12	39	14.9
06	17	6.5
03	15	5.7
04	12	4.6
09	11	4.2
02	11	4.2
08	9	3.4
01	9	3.4
11	2	0.8
05	2	0.8
Total	**261**	**100**

4.4 Discussion

This study was the first to use FRED as an exercise intervention in a clinical chronic low back pain population. The main findings of this study were that functional ability to perform problematic activities of daily living improved post-intervention by around six points on the PSFS, and pain intensity reduced by a clinically meaningful amount immediately post-intervention for 46% of participants, although this change was not significant. Overall, the SF-36 showed little change throughout the study. Compared to the UK national average, more people were above average in the MCS, and fewer were below the national average following the intervention period, although this had dropped to baseline levels by the end of the study. The PCS showed a slight improvement post-intervention, which was maintained during follow up. Compared to the national average, more people were above the national average, and fewer people were below the national average by the end of the study. Self-reported activity levels remained largely the same throughout the study. Analgesic use was low, with only 12.7% of participant-days requiring Analgesics. Analgesic use dropped during the intervention period and remained at the lower-level post-intervention. However, no statistics were carried out to determine the significance due to the skewed nature of the data.

4.4.1 PSFS

Self-reported function improved for all activity types post-intervention (figures 4.1-4.4), which is the main aim of treatment for chronic conditions (Harding & Watson, 2000). The improvements seen at A3 post-intervention were maintained through to A5 and suggested that functional ADL improvements facilitated by FRED exercise during the intervention period persist beyond the exercise period. This finding agrees with previous research (Macedo et al., 2012; Saner et al., 2015), which showed functional improvements following interventions of conventional forms of motor control exercise. This finding suggests that FRED exercise may also be helpful as a reconditioning tool for people with LBP. When considering human spaceflight specific needs, having a high level of physical function to carry out activities of daily living and operational tasks would be beneficial to the astronaut population (Hackney et al., 2015); therefore, FRED may be a beneficial reconditioning tool for post-flight astronauts. On a planetary exploration mission, this might include being able to undertake extra-vehicular activities or spacewalking outside of the safety of their spacecraft (Stuster et al., 2018). Being able to bend, lift, twist and stand successfully, as assessed here using the PSFS, would improve their operational effectiveness and safety. Future research should consider FRED exercise as a rehabilitation tool using a high-fidelity ground-based analogue of long-duration space flight, such as head-down bed rest, to test the suitability of FRED exercise for this specialist population.

The improvements in PSFS scores of the current study exceeded those reported by previous research. Saner et al. (2015) presented an improvement from 4.3±1.9 to

6.6±2.2, Macedo et al. (2012) presented an improvement from 3.7±1.6 to 5.9±2.2 when investigating graded or motor control interventions. These studies included 12 weeks of graded or motor control exercise in 106 people with sub-acute LBP (Saner et al., 2015) and eight sessions over ten weeks of graded exercise or a motor control exercise with cognitive behavioural therapy in 172 people with chronic LBP (Macedo et al., 2012). However, caution should be taken when comparing the results, as different methodologies were used in each study. One main difference is that the PSFS was not reported as different activity types but as an amalgamation of all activities to give one functional score. Another is that the previous two studies' participants started with a higher PSFS score of around four at baseline and, therefore, there may have been a ceiling effect on how far those participants could progress throughout the study. Each of the studies' duration, the total number of exercise sessions, total exercise time, and follow-up periods differed greatly, which also precludes a direct comparison of PSFS scores.

4.4.2 Numeric Rating Scale for Pain

FRED exercise may benefit some chronic LBP patients as 46% of participants reported a clinically meaningful reduction in pain at the A3 timepoint, which was not continued at follow-up. This finding suggests that FRED exercise may have an acute benefit for pain reduction but does not have a long-term effect on pain. Notably, individual pain responses to FRED exercise varied greatly, with one participant reporting a complete resolution of symptoms. However, this improvement was offset by one participant reporting a 5-point increase in pain following the intervention. Anecdotally some participants who did not experience a clinically meaningful change in pain symptoms reported pain episodes being of shorter duration post-intervention, while some participants reported that when they undertook an aggravating activity, pain episodes resolved more quickly. Unfortunately, this improved symptom resolution was not formally assessed in the current study and was an unexpected finding. Future studies should monitor both pain intensity and episode duration to elucidate this phenomenon further.

The changes in pain intensity seen at baseline may be affected by the Hawthorn effect (Sedgwick & Greenwood, 2015). It could have been that participants were happy or relieved to be taking part in the study and "finally doing something about their symptoms", as well as having access to a senior physiotherapist (DD) who was able to assess their symptoms and classify them as non-serious. This reassurance may have led to a positive bias in perceived pain by merely being reassured and included in the study (Sedgwick & Greenwood, 2015).

Encouragingly, from a possible 234 exercise sessions, only one required to be halted due to an increase in LBP during the session. This result suggests that FRED exercise is appropriate for patients with chronic LBP. Although not all participants experienced a reduction in pain intensity, even participants who experienced worsening pain symptoms showed functional improvements on the PSFS. Improvement in function and return to physical activity is considered much more important in the management of people with chronic pain than improvement in the pain itself (Harding & Watson, 2000). In this respect. Given the chronicity of the participants' symptoms (5-480 months), this study outcome can be interpreted as being very positive.

4.4.3 SF-36

The SF–36 was used to obtain a holistic picture of the participant's mental and physical wellbeing throughout the study. Some improvement in PCS was seen between the A2-A4 timepoints from 47.7±7.7 to 50.7±5. This finding agrees with

Macedo et al. (2012), who also found that physical wellbeing improved after an exercise intervention, from 43.9±10 to 53.8+12.7. However, in the current study higher PCS score was not maintained at longer-term follow-up. This finding suggests that FRED exercise had an overall positive effect on physical wellbeing while regularly used in the short term, but this was not maintained after the intervention period.

Overall, little change was seen in the MCS. This result is unsurprising as the FRED intervention did not offer a specific countermeasure for mental wellbeing but instead focused on the physical aspects of the biopsychosocial model of healthcare. The lack of change to the MCS as a result of FRED exercise is contrary to the findings of Macedo et al. (2012), who observed an SF-36 MCS improvement post-intervention from 52.9±10.5 to 57.0±10.1; however, this study included specific cognitive behavioural therapy alongside graded exercise, suggesting FRED may see more positive results if integrated into a programme that caters for the mental, as well as the physical aspects of LBP. Future research could consider FRED exercise supplemented with CBT.

Although the SF-36 was found to be appropriate for LBP in general by Bronfort and Bouter (1999) and Walsh et al. (2003), it may not be sensitive enough in this participant group, whom all displayed mild to moderate symptoms and continued to live and work in environments in which non-LBP issues may have played a more prominent role in their wellbeing at the time of data collection. For example, one participant reported that a non-back or study-related injury in the previous week affected both their physical wellbeing and positive mental health. Future FRED research could utilise an LBP specific questionnaire such as the Oswestry Disability Index to give more specific insights. Anecdotally, participants reported feeling more positive towards managing their symptoms following the FRED intervention.

However, this was not observed in the available data. Future research, therefore, may benefit from asking participants specifically about their experiences of using the FRED and their views about symptom management.

4.4.4 Self-reported activity levels and Analgesic use.

Overall, self-reported activity levels reduced throughout the study, especially outdoor tasks such as walking the dog and gardening. This reduction in outdoor activities may have been due to the time of year and weather (Tucker & Gilliland, 2007) rather than being directly attributed to the FRED intervention. These potentially confounding factors were not considered in the daily log. Therefore, it is not possible to draw a definitive conclusion with the available data. Encouragingly, the participant logs showed that during the study, two participants joined the gym, and one took up swimming in study weeks 4, 17 and 21, respectively. Personal communication received by KL suggested that, while FRED exercise may not have directly contributed to this, being part of the study with regular training sessions led to a feeling of ‘confidence’ about managing their back pain which impacted the participants’ decision to start a new exercise regime. One participant also reported returning to running; however, the exact date of this is unknown. Four participants reported a combined total of seven weeks of illness that reduced their normal activity levels, although, as previously mentioned, this may have been a natural consequence of the study spanning the autumn and winter period.

Analgesic use was generally low, representing only 12.7% of all reported participant-days. There was a slight reduction in days with Analgesic use from the intervention period, which was not maintained at follow-up. However, caution must be taken when considering these results as they were heavily skewed towards one individual (FR2016KM14) who represented over half of all analgesic use. Only one participant

(FR2106DM04) reported using less than the usual dose of non-steroidal anti-inflammatories. The current study could not determine reliably if FRED exercise leads to either a reduced need for analgesics due to LBP or a reduced dose of analgesics. A more definitive answer to this question might be provided in a patient group with a more intense pain-management regime, for example, that inpatient rehabilitation (Herrera-Escobar et al., 2021)

4.4.5 Limitations

One limitation of this study is the use of participant-reported activity levels, which are at risk of bias because they rely on individuals truthfully recording their activity levels, and not under or overestimating the time spent active (Taber et al., 2009). Underreporting of activities were discouraged using a log-keeping routine and reminder emails to ensure that the logs were filled out promptly, ensuring accurate recall. Over-reporting was reduced as much as possible by allowing participants to report all activities by type and giving credit for any activity (for example, washing dishes) instead of just sport or exercise-based activities, reducing the stigma of being inactive. Participants also understood that only specific members of the research team would see their data for analysis purposes and, therefore, they were not in competition or going to be judged. A more accurate measure of activity levels during future research could be the use of accelerometery.

Another potential limitation of the current study was statistical power. The study size was selected based on resource availability, specifically available lab and researcher time during the training period; therefore, no a priori power calculation was carried out. A Posteriori observed power shows that the study was suitably powered for the PSFS (observed power of 1.0) but underpowered for the SF-36 (observed power 0.407). While A Posteriori observed power calculations need to be treated with caution (Hoenig & Heisey, 2001; Yuan & Maxwell, 2005), having an observed power of 1.0 for the PSFS shows that the study design was a suitable measure. No other firm conclusions can be drawn for this single study for the other measures due to the relatively lower power.

4.5 Conclusion

This chapter has discussed the patient-reported outcome measures for function, pain, activity levels and analgesic use. Six weeks of FRED exercise three times per week was found to make a meaningful improvement in patient-reported function regardless of the LBP chronicity. It was also seen that pain improved in the short term for some participants. There was also anecdotal evidence suggesting that pain symptoms may resolve faster after the FRED intervention, and this needs to be investigated further. Overall physical health showed a short-term improvement, while mental health and activity levels reduced slightly by the end of the study. Analgesic use was low throughout the study. In order to determine the underlying physiological changes resulting from the six weeks FRED intervention that could have contributed to the improvements in patient-reported function, it is necessary to investigate the structural muscle changes seen in the lumbopelvic muscles that are known to be affected by chronic LBP. Chapter 5 will look at two target muscles, the Transversus Abdominis and Lumbar Multifidus, to see if and how the muscle architecture changes using ultrasound imaging.

5 Chapter 5 Ultrasound imaging in the Low Back Pain Study.

Chapter 4 highlighted the effects of FRED intervention on patient-reported outcome measures. However, whilst improvements in function were reported, the mechanisms underlying these improvements are not currently known. Therefore, this chapter will use ultrasound imaging to explore the possibility of muscle architectural changes, specifically Lumbar Multifidus (LM) cross-sectional area and thickness, and Transverus Abdominis (TrA) thickness, as a potential explanation for the improvements seen in Chapter 4.

5.1 Methods.

A detailed methodology is given of the ultrasound imaging technique in Chapter 3.4.1. Briefly, ultrasound images were collected throughout the study by one researcher (KL). All images were taken bilaterally at end-expiration in normal tidal breathing to minimise the effect of respiration on muscle size and image quality. Data were collected on the cross-sectional area and thickness of Lumbar Multifidus (LM) at rest with the participant in the prone position. In the supine position, images were collected of TrA thickness at rest and approximately 30% maximum voluntary contraction (MVC). To help participants gauge the magnitude of their contraction and ensure optimal transducer position, participants performed an unrecorded 100% MVC before the 30% MVC image collection. All participants were coached throughout the data collection to ensure optimal image quality. Video images were used to assist in muscle boundary identification for LM cross-sectional area (CSA), as differential muscle fibre movement was observable during a leg raise. However, data analysis was completed using static images, as for TrA and LM thickness.

The FRED exercise intervention used in this chapter has been discussed in detail in Chapter 4.2.1 and Chapter 3.2.3.

5.1.1 Data analysis

All images were blinded before the assessment to reduce the risk of bias. Both participant number and file date markers were masked by an independent member of the research laboratory (AW), who was not involved in the study. While a date marker was visible in the image, this did not correspond to the actual data acquisition date and, therefore, did not provide identifying information to the reviewer (KL). Image analysis was undertaken by KL using Image J software (National Institutes of Health, MD; available from https://imagej.nih.gov/ij/). Lumbar Multifidus thickness was measured from the highest point of the L4/5 facet joint to the hyperechoic fascia denoting the muscle boundary below the subcutaneous tissue. Lumbar Multifidus cross-sectional area (CSA) was measured by tracing the inner edge of the muscle border using on-screen markers and video to denote the lateral border with Erector Spinae, where necessary. Transversus Abdominis thickness was measured 1.5cm (Gibbon et al., 2013) from the tip of TrA with the thoracolumbar facia, between the hyperechoic facial lines. Examples of this are shown in Figures 5.1-3.

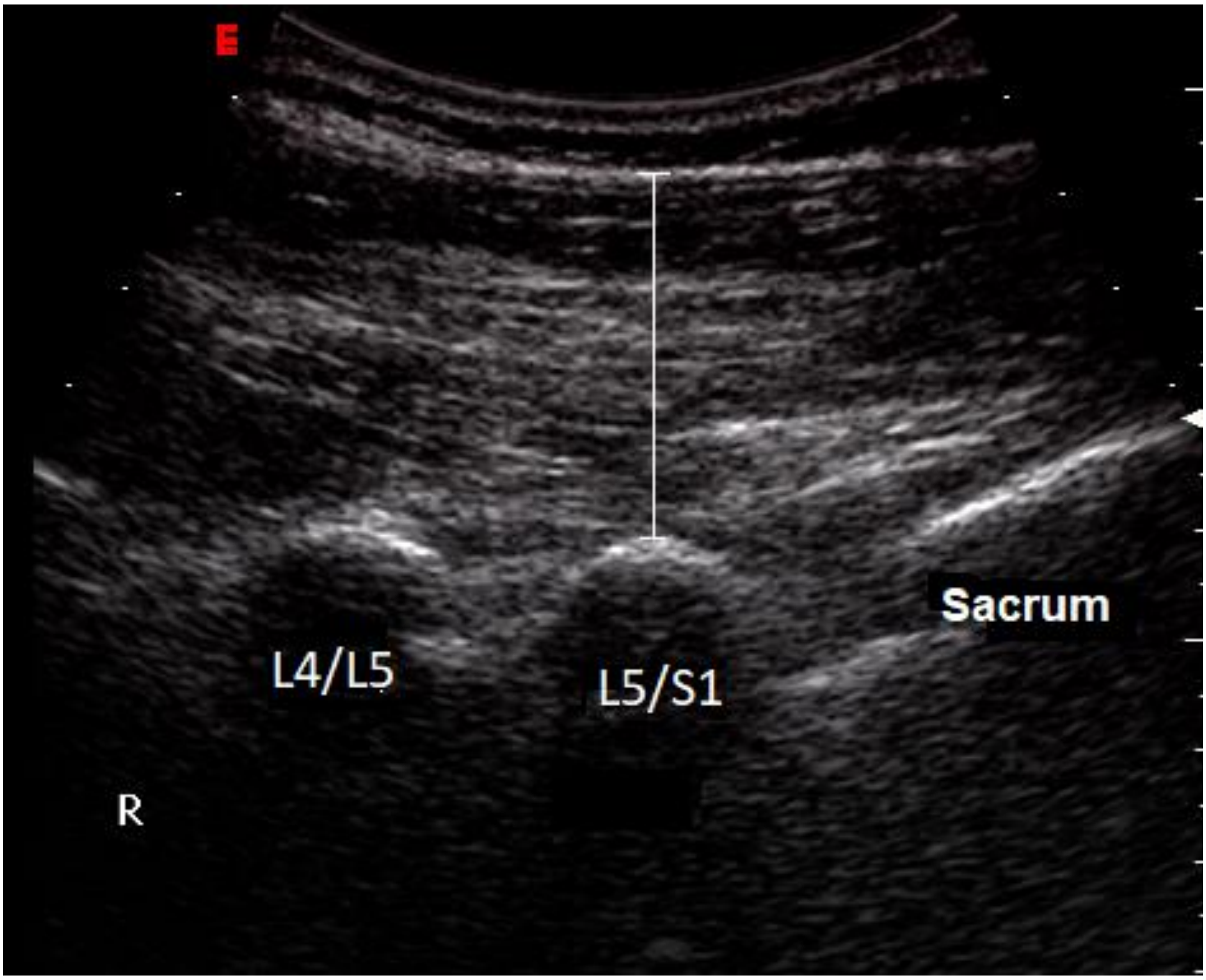


Figure 5-1 illustration of measurement taken for LM thickness at the L4/5 level between the hyperechoic bony facet joint and facia

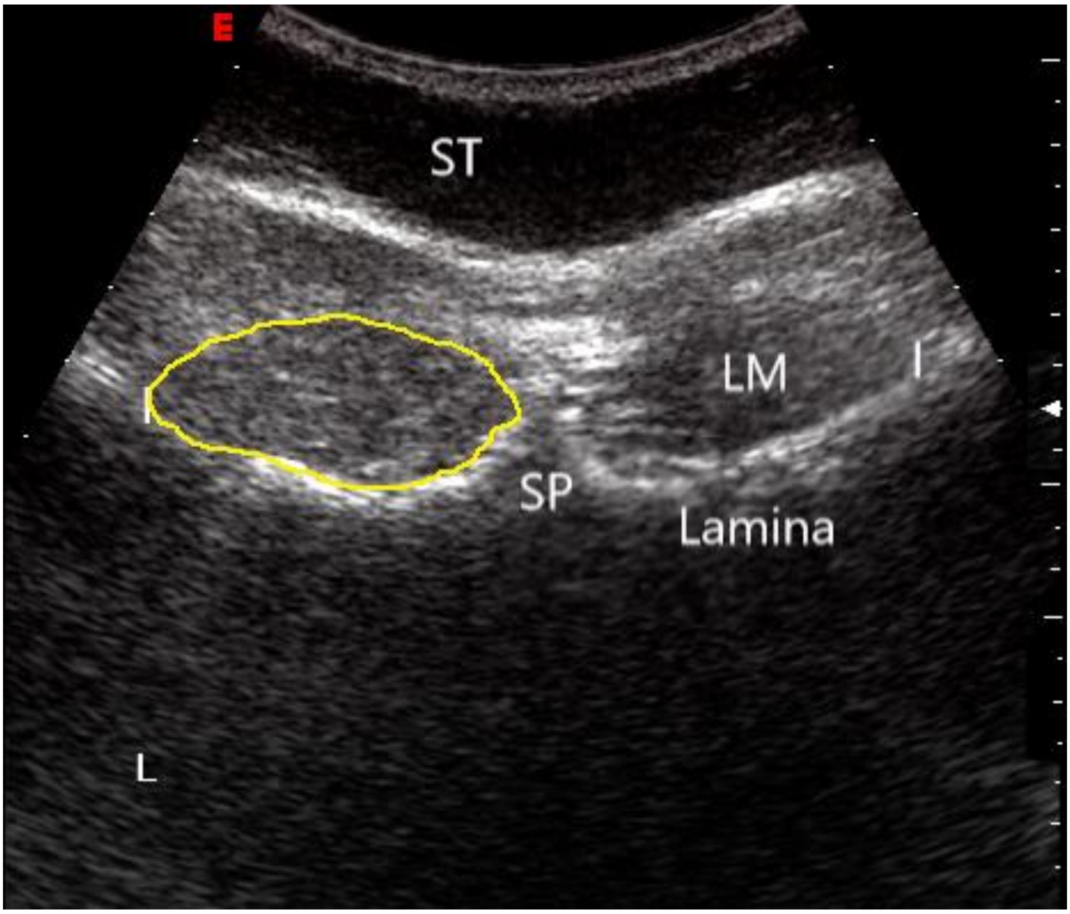


Figure 5-2 shows an example ultrasound image of LM CSA at L5/S1. LM = Umbar multifidus, ST = Subcutaneous Tissue, SP = Spinus Process

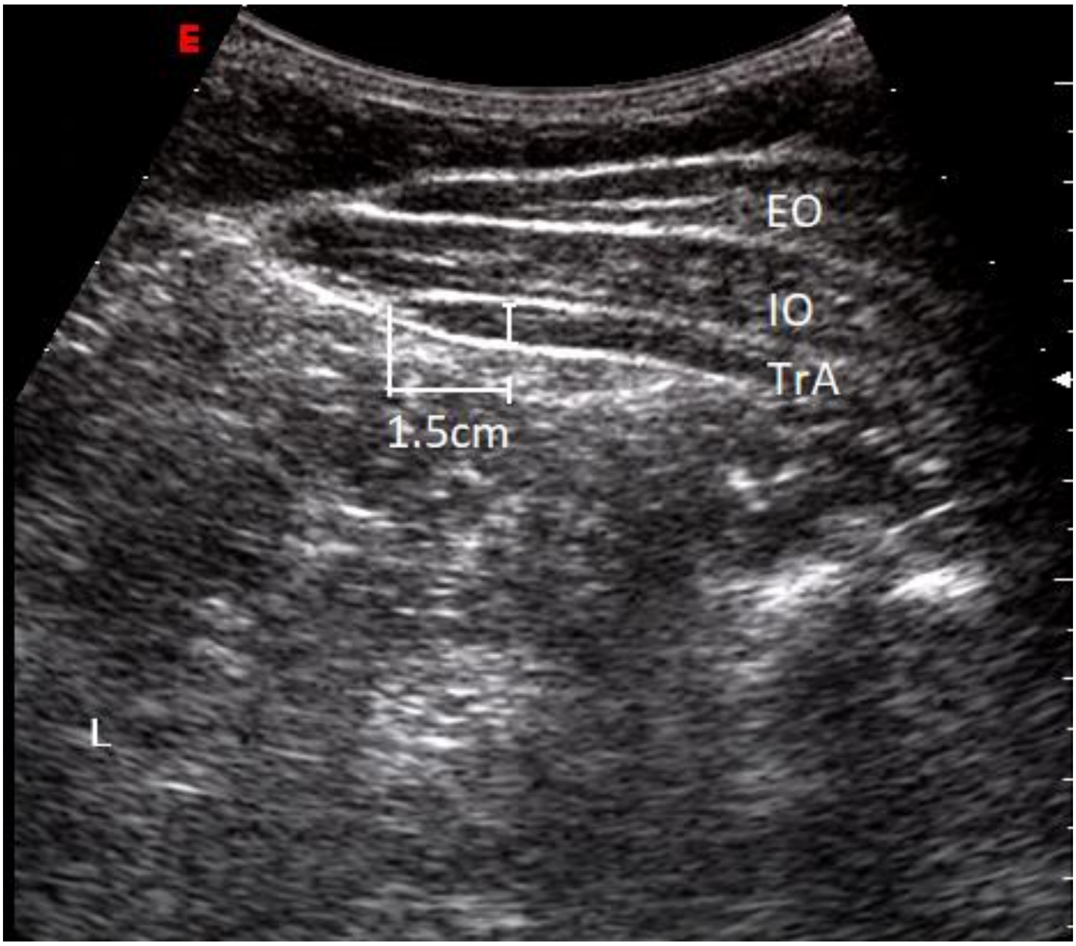


Figure 5-3 shows an ultrasound image of the TrA thickness measurement technique showing the hyperechoic facial lines between each muscle. TrA- Transversus Abdominis, IO = Internal Oblique, EO = External Oblique

All ultrasound imaging data were collected at the expected timepoint. There were some slight variations in participant positioning due to comfort and pain symptoms, and these were noted to ensure consistency between testing sessions for each participant. One participant (FR1602JE) chose to place his hands under his forehead for comfort in the prone position; this was repeated during all USI sessions. Two participants (FR1606FM and FR1614KM) experienced increased back pain in supine and therefore chose a bent-knee position, with the hips at 45° and knees at 90° for all supine data collection.

5.1.2 Statistical testing

Statistical analysis was carried out using SPSS 26 (Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Following assumption testing for normality and sphericity, all data were treated as parametric. Wilks-Lambda repeated measures ANOVA with a Bonferroni correction was carried out for side and time interactions for each outcome (LM thickness, LM CSA, relaxed TrA thickness and 30% MVC TrA thickness). Results are presented for both the left- and right-hand sides because the study participants showed a high degree of asymmetry compared to previous research.

5.1.3 Intra-rater reliability

Interclass Correlation Coefficients (ICC) were calculated for the intra-rater reliability of image measurements. ICC 3,1 was 0.845 for LM CSA measurements and 0.907 for all thickness measurements, showing good to excellent reliability for USI data (Koo & Li, 2016).

5.2 Results.

There were no significant changes seen in LM CSA or thickness or TrA thickness on either side of the body, and each comparison is shown in Table 5.1. There was a significant effect of time for left LM CSA, (Table 5.1), with a large effect size (Cohen, 1988) on the left and a medium effect size on the right (Cohen, 1988) (Table 5.2). Interestingly, the large effect size changes on the left were seen pre-and post-intervention, between A2-A3, A1 and A3 and A1 and A3; therefore, an increase in left LM CSA with a large effect was seen between baseline and immediately post-FRED, which was mostly retained six weeks post-intervention. Side*time interactions were also non-significant and are not presented here.

Table 5-1 Results of the repeated measure ANOVA with Bonferroni correction for USI measures.

Measure	**Parameter**	**Wilks lambda**	**F (hyp, error)**	**F**	**sig.**
LM Thickness	side	0.722	1,11	4.233	0.64
	time	0.972	1,11	4.233	0.96
LM CSA	side	0.936	1,11	0.755	0.40
	time	0.496	3,9	3.044	0.09
TrA 0% MVC	side	0.001	1,11	1	0.97
	time	0.335	3,9	1.511	0.28
TrA 30% MVC	side	0.500	1,11	0.576	0.46
	time	0.631	3,9	1.751	0.23

Table 5-2. Effect size and confidence intervals for USI measures. A1 = initial baseline six weeks prior to the intervention, A2 = immediately pre-intervention, A3 = immediately post-intervention, A4 = 6 weeks post-intervention.

Muscle	**Comparison**	**Δ Mean**	**CI**		**Effect size**
			Upper	**Lower**	**Cohen's d**
LM L	A1 to A2	0.01	0.38	0.36	0.01
	A1 to A3	-0.02	0.22	-0.27	-0.02
	A1 to A4	0.01	0.26	0.24	0.01
	A2 to A3	-0.02	0.85	-0.25	-0.03
LM R	A1 to A2	-0.12	0.22	-0.46	-0.10
	A1 to A3	-0.05	0.19	-0.30	-0.04
	A1 to A4	-0.13	0.15	-0.42	-0.11
	A2 to A3	0.05	0.80	0.24	0.06
CSA L	A1 to A2	0.26	0.73	0.20	0.21
	A1 to A3	0.92	1.43	0.41	**0.73**
	A1 to A4	0.84	1.41	0.27	**0.67**
	A2 to A3	-0.08	0.47	-0.62	**0.79**
CSA R	A1 to A2	0.00	0.50	0.50	0.00
	A1 to A3	0.37	1.00	0.26	0.30
	A1 to A4	0.51	1.05	0.04	0.40
	A2 to A3	0.32	0.75	0.10	**0.55**
TrA L	A1 to A2	-0.06	0.54	-0.66	-0.05
	A1 to A3	0.17	0.74	0.39	0.14
	A1 to A4	-0.32	0.23	-0.86	-0.25
	A2 to A3	0.02	0.13	0.04	0.18
TrA R	A1 to A2	-0.25	0.36	-0.86	-0.20
	A1 to A3	-0.45	0.12	-1.03	-0.36
	A1 to A4	-0.40	0.22	-1.02	-0.32
	A2 to A3	-0.02	0.16	-0.05	-0.14
TrA L 30% MVC	A1 to A2	0.41	1.21	-0.39	0.32
	A1 to A3	0.34	0.92	-0.24	0.27
	A1 to A4	0.28	0.99	-0.43	0.22
	A2 to A3	0.00	0.16	0.05	-0.03
TrA R 30%	A1 to A2	0.17	0.90	-0.56	0.14
	A1 to A3	0.45	0.87	0.02	0.36
	A1 to A4	-0.18	0.28	-0.65	-0.14
	A2 to A3	0.04	0.17	0.05	0.23

5.3 Discussion

No statistically significant results were seen in the ultrasound imaging data for the lumbopelvic muscles measured in this chapter. However, LM CSA was seen to increase with a large effect size from pre-FRED to immediately post-FRED (right side only) and between pre-FRED and six weeks post-FRED (left and right sides).

5.3.1 Muscle Architecture changes

The lack of significant change seen in this study partially agrees with previous research. Danneels et al. (2001) showed that spinal stabilisation training and spinal stabilisation training with progressive resistive exercise did not increase LM cross-sectional area at the L4 level unless the training involved a period of static activation. Weber et al. (2017) showed that FRED exercise produced a more tonic activation of the LM muscle than walking, and the muscle activation likely followed a concentric-to-eccentric pattern while weight-bearing and maintaining control of the FRED cycle. Therefore, FRED exercise may have provided short periods of isotonic contraction, followed by concentric or eccentric activation, responsible for the effects on the LM cross-sectional area. However, the shorter intervention period for this study may have meant that the muscle changes were not sufficient to produce a statistically significant result, and if given a training period equal to that of Danneels et al. (2001) of 10 weeks, a more significant result may have been observed. Interestingly, Hides et al. (2008) showed that a 13-week spinal stabilisation training intervention increased the LM cross-sectional area in elite cricketers with LBP, further supporting the idea that the FRED intervention was not of long enough duration to observe significant LM cross-sectional area change.

Recent NASA studies looking at lumbopelvic muscle and spinal deconditioning following six months on the International Space Station showed that the paraspinal muscles atrophy despite many inflight countermeasures does not return to pre-spaceflight CSA following rehabilitation (Chang et al., 2016). Spaceflight also induces a reduction in lumbar lordosis (Bailey et al., 2018). It was suggested that LBP development in astronauts is likely due to muscular changes in-flight rather than spinal disc changes (Harrison et al., 2018). As such, the increased LM CSA seen here is encouraging as it suggests, along with previous findings that FRED exercise elicits an increase in lumbar lordosis in asymptomatic and symptomatic users (Winnard et al., 2017a), that a FRED intervention may act to reverse spaceflight-induced paraspinal muscle atrophy and restore lumbar lordosis.

TrA and LM thickness showed no significant change throughout the study, surprising as FRED was expected to produce a hypertrophic effect by recruiting LM and TrA during use. However, there are several explanations as to why this may not have happened. One possibility is that 15 minutes of FRED exercise three times a week did not provide a sufficient exercise stimulus to mediate muscle growth, and a more intense exercise protocol may achieve this (Schoenfeld, 2013). There is a weak correlation between total exercise time and left LM cross-sectional area ($R = 0.35$) and a moderate correlation between right LM cross-sectional area and total exercise time ($R = 0.64$), suggesting that despite the lack of statistically significant results, FRED exercise does have some effect on the LM muscles.

Another possibility is that muscle architecture changes are not linked to the meaningful clinical improvements noted in Chapter 4. For example, Willemink et al. (2012) found no link between functional improvements and muscle size after ten dynamic isolated lumbar extension exercises. This idea is supported by research published after the data collection completion of the LBP Study by Andersen et al. (2018), who found no significant changes following 12 weeks of either general exercise for the low back or focused spinal extensor exercises in a population of helicopter pilots who experienced LBP. Larivière et al. (2018) found that an eight-week spinal stabilisation exercise intervention did not result in LM thickness changes between S1 and L4, despite a clinically significant reduction in pain intensity and a clinically meaningful increase in the Oswestry Disability Index, signifying an improved quality of life for participants. These findings suggest that the positive effects of exercise in chronic low back pain may not be linked to the muscle architecture and that the potential mode of action has yet to be elucidated. In the current LBP study, another factor that needs to be considered is the level of muscle asymmetry in this population, discussed in section 5.4.2.

5.3.2 Muscle Asymmetry

Normal asymmetry in a healthy population between left and right LM cross-section area is <10%, and <21% for TrA thickness (Rankin et al., 2006). However, some participants showed asymmetry beyond these norms. Which was maintained by, and sometimes increased, after the FRED intervention. Frantz Pressler et al. (2006) showed that LM cross-sectional area at the S1 level was stable when measured between one and four days from baseline measurement. They also calculated that the minimum difference needed between each measurement for a 95% confidence interval was 0.74 cm^2 for actual anatomical change. In the current study, changes of this magnitude were seen in the baseline and after the intervention. This change suggests that, in an LBP population, LM CSA may be more fluid than in healthy populations. Another possible confounding factor affecting LM cross-sectional area is that posture was discussed by the senior physiotherapist (DD) when discussing the participants' experience of back pain during the initial physiotherapy treatment, which may have alerted the participant to their postural issues, allowing the participants to 'correct' previously poor posture.

The observed asymmetry could also result from pain inhibition leading to muscle atrophy on the affected side (Hides et al., 1994) or could be caused by overuse as a protective mechanism leading to hypertrophy (van der Hulst et al., 2010). In the current study, when looking at individual changes, those who started the study with LM hypertrophy tended to lose cross-sectional area. Conversely, individuals who had smaller LM cross-sectional areas at the beginning of the study were more likely to experience hypertrophy. This phenomenon can be seen in Figure 5.4 for each side and 5.5 for overall change. This result suggests that FRED exercise had a normalising effect on muscle function, which encouraged the muscle to adapt to use. This idea is supported by the results of Caplan et al. (2014) and Weber et al. (2017), who found that FRED encourages a more normal tonic activation of paraspinal muscles compared to over-ground walking. This finding suggests that FRED may be a suitable rehabilitation tool for patients who exhibit both over-and underuse of LM by encouraging more effective muscle coordination and control, although more research is needed to confirm this.

As CSA was both gained and lost by the same magnitude, the overall group effect was minimal. However, it is unclear why some participants gained LM CSA and some lost LM CSA. The average total exercise time was 176±10 minutes in the reduced group and 177±12 minutes in the gained group. Additionally, the average time since the start of LBP was 11±10 years in the reduced group and 13±12 years in the gained group, suggesting that neither symptom duration nor total exercise time was a predictive factor in who would benefit from FRED exercise. Future FRED research may benefit from a larger group intentionally split into over- and under-use groups following the initial clinical screening to confirm that FRED has a normalising effect in each group. This grouping may also account for the lack of statistically significant results.

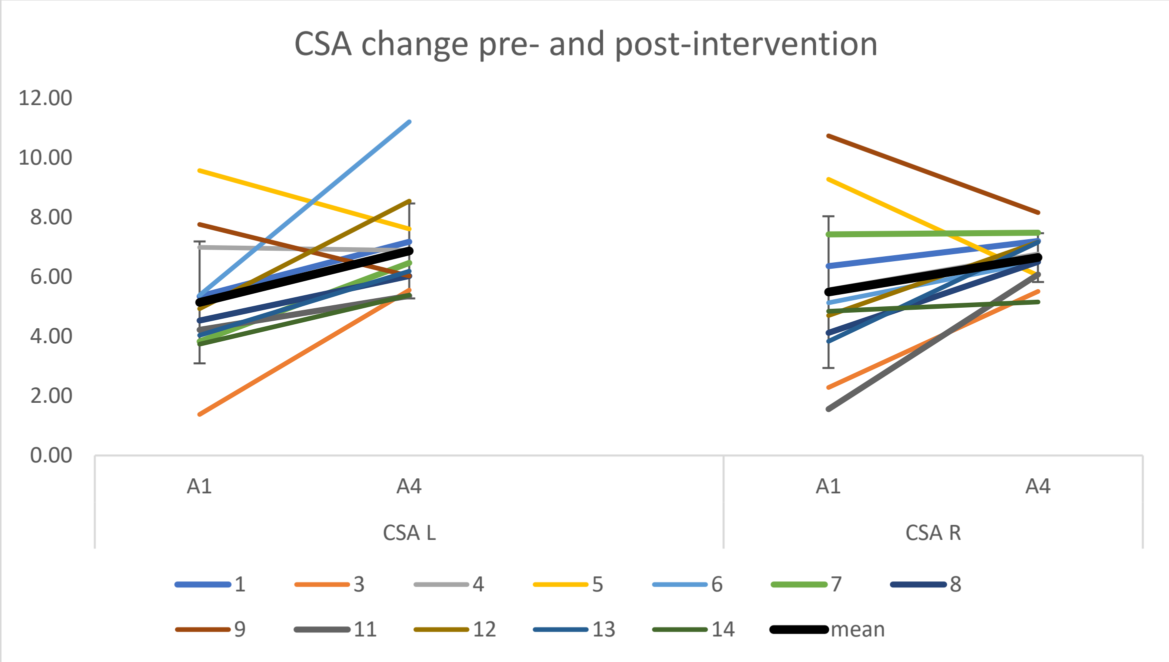


Figure 5-4 shows the individual responses to FRED exercise pre-post intervention.

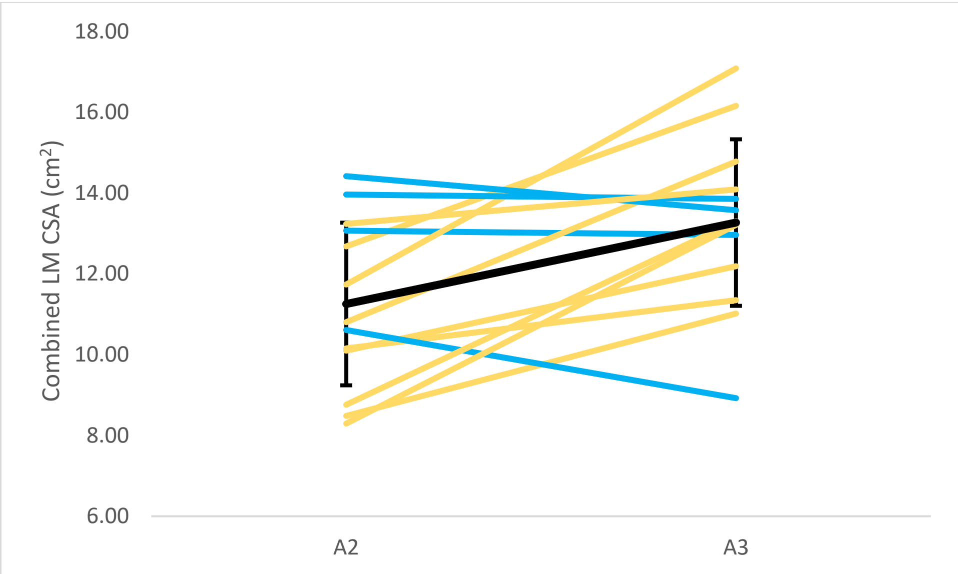


Figure 5-5 shows the total change in bilateral LM CSA pre-and post-intervention, where people starting with higher total LM CSA tended to lose CSA following FRED (blue) and people with smaller total LM CSA tended to gain CSA (yellow). Overall, most participants gained CSA after the FRED exercise. Black = mean

As it was initially expected that FRED exercise would illicit bilateral changes in muscle architecture, the FRED data were interrogated further to see if an explanation could be found for the asymmetric LM cross-sectional area results, and these are discussed in the next section more detail.

5.3.3 FRED cycle analysis.

Following the unexpected left-sided bias seen in the LM cross-sectional area changes and observations made in the lab during training, further analysis was undertaken of the FRED cycle to determine if the exercise was responsible for the results seen. A lateral preference was suspected following reports of limb fatigue and discomfort during extended FRED use. Therefore, it was hypothesised that the muscle hypertrophy seen in the left LM was linked to lateral preference, which may be linked to handedness (Frantz Pressler et al., 2006) and would manifest in greater FRED control, shown as a minor variation from the target frequency of 0.42 Hz for the half of the cycle where the favoured leg was in the control position.

Like the gait cycle, the FRED cycle can be broken into smaller components defined by the crank position. The FRED crank provides 1000 data pulses per cycle, with an extra pulse produced when the right footplate is in the top-dead-centre position. By counting 500 pulses, the bottom-dead-centre point can also be determined. Between top-dead-centre and bottom-dead-centre, the right limb is in the forward position 'falling' downwards, and the left is in the posterior position, acting as the breaking or controlling limb between the bottom-dead-centre and top-dead-centre the reverse is true. This cycle divide is shown in Figure 5.5.

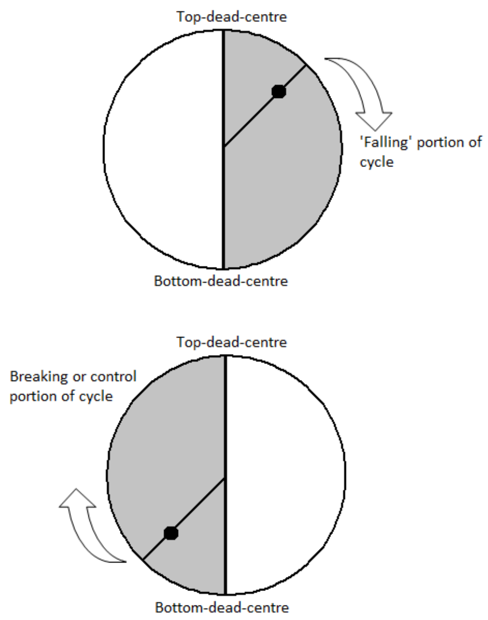


Figure 5-6 The FRED crank cycle broken into the 'falling', or non-control leg, and 'breaking', or control leg, sections are defined between the top-dead-centre and bottom-dead-centre.

Previous research in cycling has shown that a lateral preference is present in most riders, with lateral asymmetry increasing at lower cadence and workload, which reduces at higher speeds and workloads, while around 45% of people can be expected to exhibit a right-sided lateral preference (Carpes et al., 2010).

For this analysis, ten complete FRED cycles were taken from the beginning of the 1-minute data collection during the BDC (A1) time point. Each cycle was manually divided into 500 data pulses ± five pulses, and an average of the FRED frequency was calculated using LabView. Incomplete cycles, or those containing more than 1000 data pulses due to backwards pedalling after a loss of balance, were omitted, and the next whole normal cycle was used. Results were calculated as the percentage difference from the target frequency of 0.42 Hz, as this was the predefined target frequency which the participants could see in the middle of the screen. The left-foot controlled portion had a 12.33±8.75% difference between the actual and target frequency, while the right-foot controlled portion had a 6.34±5.12%

difference, with a large Cohen's d effect size of 0.9. Handedness as the main factor for the FRED side-preference was not supported in the current data; ten participants were right-handed, with only one showing right-side preference, and one participant was left-handed, who did have a left-side preference. However, the sample size was too small to draw any definitive conclusions. The participants' apparent ability to deviate less from the target frequency when the right leg was in the control portion of the cycle suggests that FRED exercise may have a lateral bias where LM activation leads to the single-sided hypertrophy observed contralateral the side which was closest to the target frequency. A more detailed analysis with a larger cohort of left-and right-handed individuals, with electromyography of the leg and trunk muscles, would be needed to confirm this.

5.3.4 Limitations

The LBP study had several limitations which may have affected the outcome. The exercise intervention may not have provided enough exercise stimulus to encourage muscle architectural changes in the lumbopelvic muscles, especially TrA (Schoenfeld, 2013). When designing the study, care was taken to consider the participant's needs in the form of time away from work to undertake the study, their LBP's chronic nature, and the laboratory resources required to complete the training sessions successfully. However, a more intense intervention programme may better elicit these changes during future research. Additionally, the use of voluntary contractions during ultrasound image acquisition was a limitation as the measurement relies on each participant's willingness and ability to reproduce contractions accurately. It was not possible to confirm that each contraction was precisely at the 30% MVC level, although efforts were made to control this. External stimuli, such as peripheral magnetic stimulation (Masse-Alarie et al., 2013), may have allowed for more reproducible results. However, this technique has not been widely studied in LBP patients and can cause pain and discomfort (Kanjanapanang & Chang, 2019), which, in conjunction with the intramuscular EMG used during this study, made it inappropriate the current research.

5.4 Conclusion

This chapter has shown that FRED exercise did not produce statistically significant changes in the thickness of the Lumbar Multifidus or Transversus Abdominis in a chronic low back pain population. However, LM cross-sectional area was approaching significance and showed a large effect size, although individual variation and muscle asymmetry also need to be considered. Total exercise time was weakly correlated with the changes seen in LM cross-sectional area. Therefore, future studies still need to consider the muscle architectural changes when completing FRED exercises. The next chapter will the final data from the terrestrially based clinical population model by considering the impact that the FRED intervention has on dynamic movement control and postural control

6 Chapter 6 Neuromuscular control in LBP

Chapter 5 discussed the muscle architectural changes seen following The FRED intervention period, and these now need to be related to postural control. Countermeasures for postural control are essential in LPB populations because research consistently shows that chronic LBP is associated with poorer outcomes and less able to react to perturbations compared to healthy controls, while LBP is an independent risk factor in falls (Frost & Brown, 2016; Marshall et al., 2016). FRED exercise's primary role is to actively recruit the lumbopelvic muscles; however, FRED also offers a postural challenge and may influence balance as a by-product of use. Therefore, this chapter will explore the postural control changes following FRED intervention by analysing both static balance and FRED movement variability.

6.1 Methodology

A detailed methodology is discussed in Chapter 3.2. A brief synopsis for the static and dynamic postural control tasks is given here. Please note that although the convention to subtext the force direction (Fy and Fx), this thesis has left the direction as main text to improve readability on a screen.

6.1.1 Static Balance

Static balance tasks included bilateral eyes open (BEO) and closed (BEC), single-leg standing eyes open (MEO) and closed (MEC), and Most participants failed to maintain their balance for the 20 seconds required for analysis in the MEC and bilateral on-blocks conditions, so they were excluded before analysis. The participants stood sideways on the force plate to accommodate data collection equipment in the lab. Consequently, the Fx direction on the force plate represents the mediolateral direction (M-L), and Fy represents the A-P direction, shown in Figure 6.1.

Static balance data were extracted and analysed in 20-second bins using a bespoke Matlab (The Mathworks Inc, Natick, Massachusetts)program, using the methodology described in Lakie et al. (2003), in which the Centre of Pressure (CoP) force plate data were divided into unidirectional anteroposterior (A-P, Fy) and mediolateral (M-L, Fx) directions. Total sway path length was determined using the sum of individual sway lengths in the A-P and M-L directions for each 20 second period. Zeroing of the force plate was completed before the start of each participant, and identical foot placement was ensured between testing sessions by standing on footprints drawn on non-slip fabric on the force plate surface.

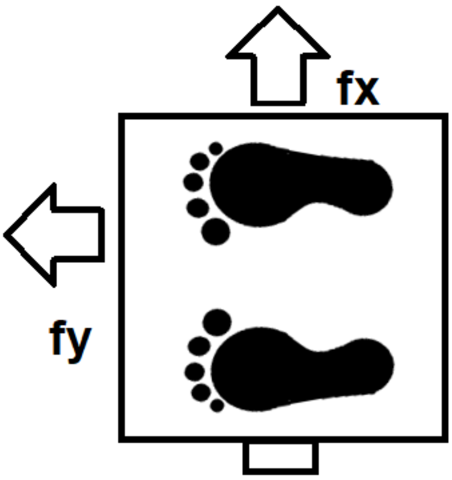


Figure 6-1 shows the anatomical and force plate directions in this experiment. Participants were rotated 90° compared to the normal force plate position to accommodate equipment placement in the lab; therefore, force plate x and body x directions are not aligned in this experiment.

6.1.2 Dynamic balance

An assessment of dynamic balance was made by measuring movement variability during FRED exercise. Movement variability, or the standard deviation of the movement compared to the mean frequency for 1 minute, was used as a proxy measure of movement control, with a minor movement variability representing better movement control. The fourth minute of data was analysed at A1-A4, and on each training session throughout the intervention period, using LabChart (AD Instruments Australia) and Microsoft Excel 365 (Microsoft Corporation, Redmond WA)

Data analysis

After assumption testing, the static balance data were treated as normally distributed parametric data. A repeated-measures ANOVA with post hoc Bonferroni correction was carried out using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). A $p = 0.05$ was used for significance. Cohen's d effect sizes were calculated using Microsoft Excel 2016 with thresholds for size as Cohen (1988) defined.

6.2 Results

6.2.1 Static Balance

A repeated-measures ANOVA with Bonferroni correction showed that the total sway path length in the BEOx (M-L direction) condition had a significant main effect of time (Wilks' Lambda = 0.336, $F(3,9) = 5.931$, $p = 0.16$). Post hoc pairwise comparisons showed that A3-A4 significantly reduced path length ($p = 0.04$) with a small effect size ($d = -0.35$), shown in Table 6.1. There were no other significant results in either the A-P or M-L direction for any other balance condition. There was a strong (Mukaka, 2012) inverse correlation ($r = -0.73$) between change in the NRS pain intensity score and change in sway path length between A3 and A4 in the BEOx and BEOy condition, shown in Figures 6.3 and 6.4, meaning participants with increased sway path total length reported improved pain scores. There was also a moderate (Mukaka, 2012) correlation ($r = 0.65$) in the BEOx condition between changes in PSFS and total sway path length, meaning participants who showed an improvement in PSFS scores also showed a longer total sway path length.

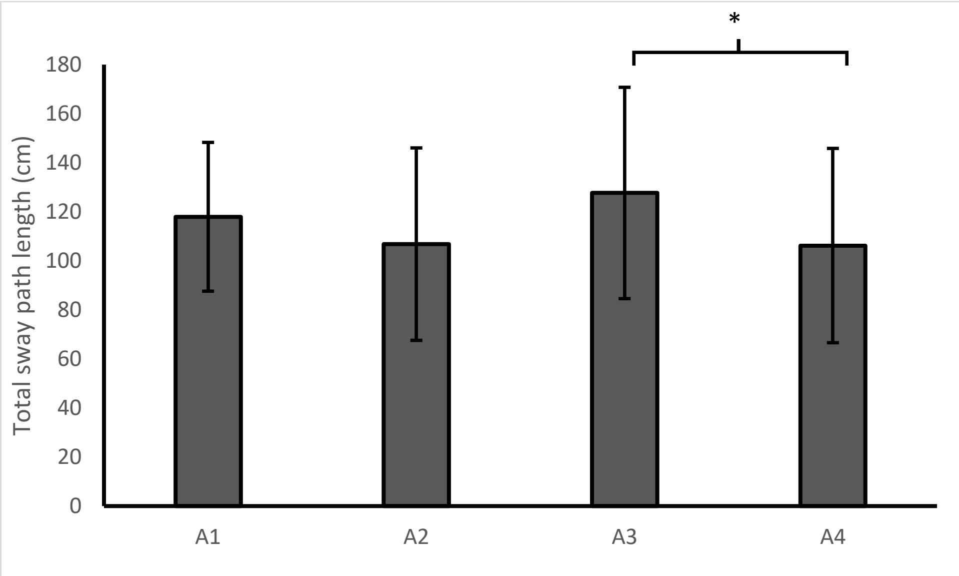


Figure 6-2 shows the mean and SD of BEOx total sway path length. * Denotes a significant change.

Table 6-1. shows the significance, mean change, confidence interval and effect size for the BEO, BEC and MEO balance conditions in the x and y-direction

				Confidence Interval		
Timepoint	**condition**	**significance**	**Δ mean**	**lower**	**upper**	**effect size**
1 to A2	BEOx	0.77	11.15	-10.56	32.87	-0.21
2-A3		0.56	-20.86	-57.24	15.52	0.33
2-A4		1.00	0.59	-36.13	37.31	-0.01
3-A4		**0.04**	**21.40**	**0.84**	**42.06**	**-0.35**
1 to A2	BEOy	1.00	4.46	-11.40	20.33	-0.14
2-A3		1.00	-1.99	-19.87	15.88	0.07
2-A4		1.00	6.69	-12.80	26.19	-0.22
3-A4		0.09	-8.69	-18.39	1.01	-0.31
1 to A2	BECx	0.49	-37.50	-100.43	25.44	0.36
2-A3		1.00	2.29	-54.70	59.28	-0.02
2-A4		1.00	4.02	-47.81	55.86	-0.04
3-A4		1.00	1.74	-32.30	35.78	-0.02
1 to A2	BECy	0.26	-19.70	-47.33	7.93	0.43
2-A3		0.18	10.54	-3.03	24.12	-0.26
2-A4		0.78	11.42	-11.02	33.86	-0.28
3-A4		1.00	0.88	-18.41	20.17	-0.02
1 to A2	MEOx	0.67	39.16	-33.32	111.63	-0.31
2-A3		0.70	-30.96	-89.22	27.30	0.22
2-A4		1.00	7.49	-50.46	65.43	-0.06
3-A4		0.29	38.45	-16.93	93.82	-0.27
1 to A2	MEOy	1.00	47.65	-70.15	165.46	-0.28
2-A3		1.00	14.89	-77.42	107.20	-0.11
2-A4		1.00	36.24	-45.94	118.43	-0.26
3-A4		1.00	21.35	-45.10	87.80	-0.17

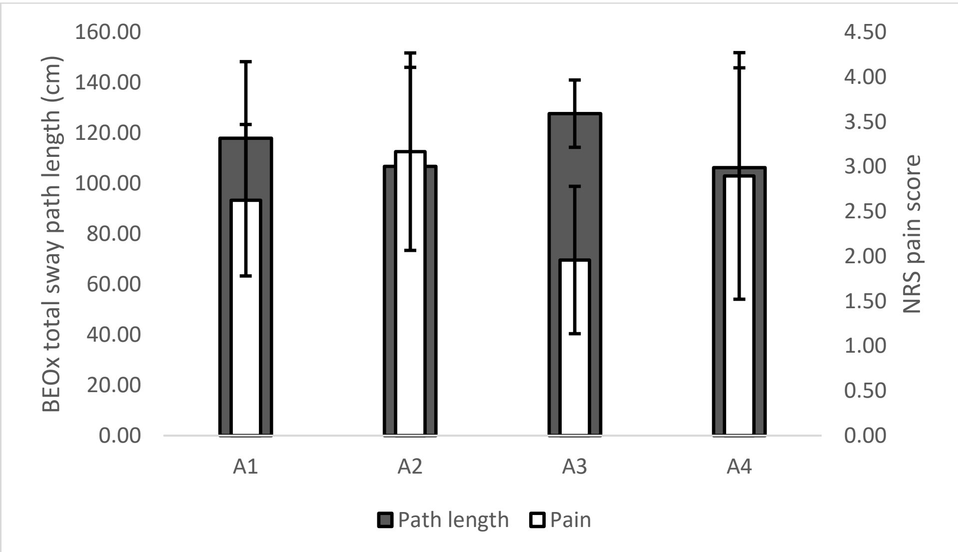


Figure 6-3. shows the mean± SD BEOx total sway path length and NRS scores. Longer path lengths correlate strongly with lower pain scores.

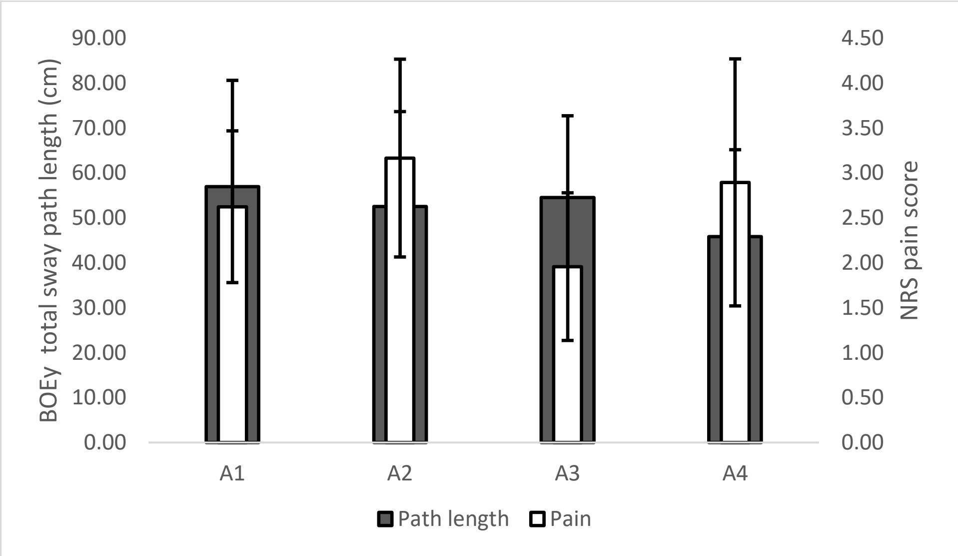


Figure 6-4. shows the mean and SD BEOy total sway path length and NRS scores. Longer path lengths correlate strongly with lower pain scores.

6.2.2 Dynamic Movement variability

A repeated-measures ANOVA with Bonferroni correction found a significant main effect of time on movement variability (Wilks' Lambda = 0.911, F (3,10) = 34.031, p = 0.001). Post hoc analyses showed significant differences between every test time point, suggesting that participants continued a learning curve throughout the study. Closer inspection of the data suggests that A1 and A2 had similar movement variability; weeks 1-3 and weeks 4-6 also shared similar variability, followed by an increase at A3 and a reduction at A4. This is shown in figure 6.5.

During the FRED task, there was a significant reduction in FRED frequency (Wilk's Lambda = 0.301, F(3,10) = 7.734, p = 0.006) and post hoc testing showed a significant reduction in average movement frequency post-intervention compared to pre-intervention, with an average target frequency of 0.42±0.12 Hz pre-intervention and 0.36±0.06 Hz post-intervention. There were no significant changes seen between the two pre- and two post-intervention time points, as shown in Table 6.2.

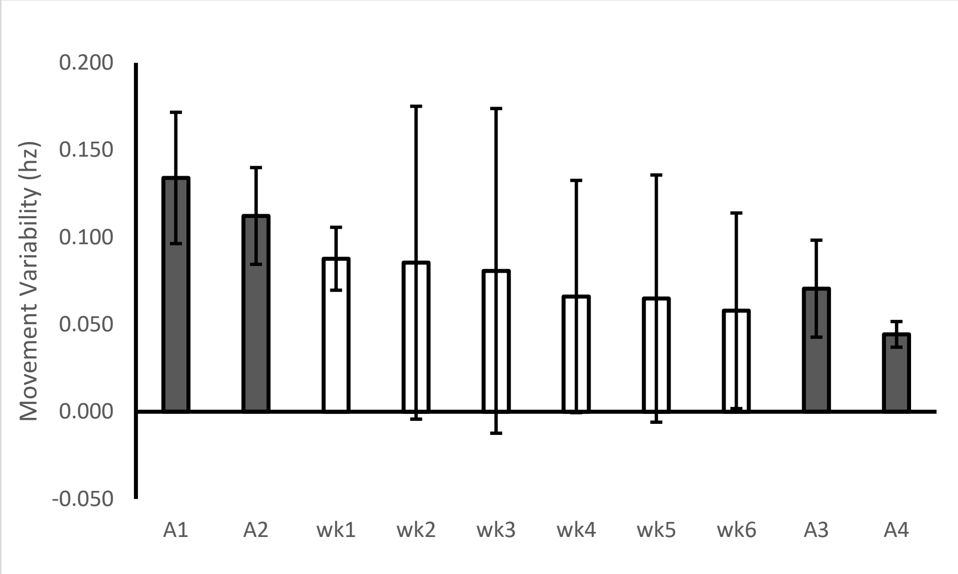


Figure 6-5 shows the average movement frequency, significant improvement post-intervention, and no significant difference between the pre and two post-intervention time points.

Table 6-2 Movement variability changes throughout the LBP study, including weekly averages. The presence of iEMG electrodes may cause the spike at A3

Timepoint	Mean Difference	Sig.	Confidence Interval Lower Bound	Upper Bound
A1 to A2	-0.007	1.000	-0.037	0.024
A2 to A3	0.064	0.005	0.019	0.109
A2 to A4	0.068	0.005	0.019	0.117
A3 to A4	0.004	1.000	-0.040	0.048

6.3 Discussion

The main findings in this study were that static balance showed a significant increase in total sway path length between A3 and A4, with strong and moderate correlations with a reduction in pain at that timepoint. In the dynamic balance task, the participants showed a significant reduction in average movement frequency post-intervention from 0.42Hz to 0.36Hz, and significant reductions in movement variability at all time points. Movement variability tended to stay roughly the same for around nine sessions (3 weeks) before dropping, suggesting that at lasted nine FRED sessions were needed to elicit an improvement in motor control. There was an increase in movement variability at A3 compared to the previous training week and following data collection, which may be due to the presence of iEMG electrodes in that session, although the data are not discussed in this thesis.

Impaired balance in LBP may result from different muscle activation timing, sequence and reduced overall co-ordination (Frost & Brown, 2016) and has been identified as an independent risk factor in falls (Marshall et al., 2016). These findings suggest that balance changes in the LBP population may also elucidate changes in balance for astronauts who show altered balance and co-ordination post-flight (Casellato et al., 2017; Mulavara et al., 2018). Total sway path length was chosen to study the centre of pressure (CoP) displacement because it is a derived measure that accounts for changes in sway velocity and duration, which are consistent and reproducible measures of CoP displacement (Raymakers et al., 2005). Changes in the CoP path correspond to the neuromuscular control of postural stability because it characterises the position of resultant ground reaction forces used to maintain postural stability (Ruhe et al., 2011). The current study utilised the approach of (Mok et al., 2004), in which participants were presented with balance challenges with increasing difficulty with both eyes open and eyes closed conditions.

6.3.1 Static Balance

The bilateral eyes-open M-L total sway path length (BEOx) increased significantly at the A3 data collection point before returning to the pre-intervention level at the A4 time point. Reeves et al (2006) suggested that people with chronic low back pain adopt a braced spinal posture during balance tasks, resulting in an overall high level of spinal stiffness; this may lead to reduced postural sway, which agrees with the research of Salavati et al. (2009) who found LBP participants exhibited less postural sway than healthy controls. An increase in postural sway path length at A3, which also corresponds to the lowest recorded pain symptoms, suggest that the participants were moving more freely and exhibited less bracing and spinal protection postures immediately after the FRED intervention. Increases in postural sway can be seen as a negative attribute (Caffaro et al., 2014; da Silva et al., 2018). Strang et al. (2011) argue that whether the reduction or increase in postural sway is beneficial depends on the reference of the experiment. In this case, the strong correlation with a reduction in pain suggests it may be beneficial. Interestingly, a significant increase in sway path length in the M-L direction suggests this was a factor of FRED exercise, as a central component of the FRED movement is a lateral weight transfer when the limbs transition from acting as a load-bearing break to the freefalling non-weight-bearing limb. The FRED cycle is discussed in more detail in chapter 5.4.3.

Previous research has shown that people with LBP experience more significant challenges in maintaining balance (da Silva et al., 2018; Mok et al., 2004) and may, therefore, be more prone to falling or an injury after an unexpected perturbation (Marshall et al., 2016). Behennah et al. (2018) found that people with LBP specifically experienced balance issues during the extensor dominant (or posterior) portion of the star excursion balance test (SEBT). They found that 19% to 38% of balance variance from healthy controls could be explained by reducing spinal extensor muscle strength. Interestingly they did not find muscle endurance was a factor when considering balance variance. Oyarzo et al. (2014) found that people with LBP used more energy and had a greater CoP displacement than healthy controls, suggesting that people with LBP need to work harder to maintain balance, even in quiet bipedal standing.

In the current study, the lack of significant results in everything except BEOx condition, arguably the easiest balance task as it included both a broad base of support and visual input, is inconsistent with previous research. Previous research found more challenging postures, with loss of sight and reduced proprioception, increase the CoP measures in LBP populations (Bergquist et al., 2019; da Silva et al., 2018; Koch & Hänsel, 2019). However, in their review of LBP balance research Koch and Hänsel (2019) also note that research findings are inconsistent across studies due to methodology and participant symptomatology. Some intervention studies have also reported non-significant findings post-exercise intervention (Bento et al., 2015; Berenshteyn et al., 2019; Shamsi et al., 2017).

One potential reason for the lack of post-intervention changes in the current study is task specificity and skills transfer. There is disagreement in the literature on whether balance skills are specific to the task being performed or are transferable skills. For example, Hirase et al. (2015) found that, in a group of 93 older Japanese adults, balance training for two hours a week for four months using a foam balance pad improved overall balance performance of both the single leg and double leg stance test. They found observable changes after only eight weeks compared to controls who did the same exercises on a stable, non-compliant surface. However, a study by Giboin et al. (2015), which compared the effect of two different balance training devices on 40 healthy young adults, found that only the trained activity improved and that there was no skill transfer into the non-trained task, even when the non-trained task was functionally similar to the training device. This observation suggests that because the static balance task was sufficiently different from FRED movement, there was no skill transfer between the two.

The lack of significant changes to CoP measures in other LBP studies (Bento et al., 2015; Berenshteyn et al., 2019; Shamsi et al., 2017) suggests that in the current study, participants' LBP had minimal impact on their balance and postural control. Therefore, a ceiling effect meant that no significant change was observable in this population compared to their performance without healthy controls. Mazaheri et al. (2013) supported this idea, showing an increase in postural sway may be expected in some, but not all, LBP patients and that testing protocols and reporting differences make it difficult to draw firm conclusions on the effect of LBP on balance in general.

Bergquist et al. (2019) carried out a systematic review of clinical balance tasks used in young senior adults and found that 69 different balance tests were reported, of which 28 specifically aimed to study static balance. They concluded that more challenging balance postures, such as those on an unstable base of support or a reduced base of support, should be used when possible. da Silva et al. (2018) supported this view and found that single-leg standing (SLS) is a suitably sensitive measure for use in people with chronic LBP, although the current study did not find any significant changes in single-leg stand condition**.** Also, in the current study, participants performed poorly in more demanding tasks, making meaningful analysis impossible. This suggests that a compromise between physical capabilities and test sensitivity is needed. Most participants in this study completed a single-leg-stand with their eyes open. Therefore, the lack of significant changes seen despite the sensitive tests used could mean that FRED has minimal impact on static balance control in an otherwise healthy working-age adult population with LBP. However, limitations need to be considered, discussed in section 6.5, before a firm conclusion is made.

6.3.2 Dynamic movement control

Elliptical trainers are understudied in all aspects of exercise physiology research, with only two previous papers (Damiano et al., 2016; Jackson et al., 2010) identified using traditional elliptical trainers in rehabilitation, making a comparison to previous research difficult. Additionally, the near-zero friction and the need to control FRED footplates, instead of working against resistance in a standard elliptical trainer, make a direct comparison difficult and different modes of activity. Jackson et al. (2010) used a regular elliptical trainer intervention for three elderly stroke patients twice a week for eight weeks. The research found improvements in the Berg balance scale; however, some changes were below the minimal clinically important difference for this test. The small sample size limited the usefulness of this study; however, it does suggest that elliptical trainers may be a helpful balance intervention for some patients, especially those with severe balance and mobility issues. Damiano et al. (2016) found that high-cadence elliptical trainer intervention in 24 participants (12 healthy control and 12 with traumatic brain injury) improved balance performance after an eight-week program. This research supports the idea that elliptical trainers can be a useful rehabilitation tool that can influence balance outcomes.

The current study using movement variability as an ersatz measure of neuromuscular control of postural stability found that FRED exercise was able to positively influence movement control, as participants continuously reduced the movement variability and average movement frequency during the study. There is an interesting increase in movement variability at A3, suggesting less movement control. There are a few potential reasons for this. One probable cause is that the participants moved from a smaller (harder) crank in week six back to the largest crank at A3, and therefore needed to relearn how to use FRED at the easier crank setting. A second possible reason could be the inclusion of intramuscular EMG at the A3 timepoint, which was part of a concurrent study, which is not discussed in this thesis. However, this seems unlikely to have had a significant role in the increased movement variability because iEMG was also included at the A2 time point without an apparent adverse effect.

Interestingly, total exercise time correlated strongly with improvements in movement variability (r = 0.7), while the crank setting did not affect it. However, because time was reduced as the crank setting was increased, paradoxically, people who improved the most experienced less overall exercise time. Further study is needed, which looks at the effect of the total exercise time on the paraspinal muscles and balance without crank changes.

All participants, regardless of the physical ability or LBP symptomology, maintained an average frequency of 0.42Hz after only eight minutes of FRED exposure, suggesting that this frequency did not provide enough of a control challenge in this population. Reducing the starting target frequency to the average of the trained LBP population in future research (0.36 Hz) may help the FRED exercise be more effective by providing a more prominent, evidence-based postural control challenge at the start of the intervention period. Overall, the study showed that FRED was effective at improving both average frequency and movement variability after the intervention period, and it, therefore, has a potential rehabilitation role for populations where movement control is impaired; this agrees with previous research using standard elliptical trainers (Damiano et al. 2016 and Jackson et al. 2010).

6.4 Limitations

The current study experienced several limitations that may have impacted its ability to detect a meaningful change in static balance. One limitation could be the study population. Most of the participants had mild to moderate LBP and impairment associated with that LBP. Therefore, their balance may not have been impaired enough to be detected in the current trial. In a population with more severe impairment, such as post-flight astronauts or those with severe limitations and LBP, FRED may have a more observable effect. Another consideration is that the participants could not complete the most sensitive test of single-leg standing with eyes closed balance tasks, meaning potentially important insight from the analyses was lost. Another potential limitation is that the balance tasks were all completed in standing and involved the lower limb kinetic chain, as the lower limbs also have a role in maintaining balance (Radebold et al., 2001). It may be that the participants were able to successfully compensate minor influences from the spinal musculature during the tasks by adapting at the knee and ankle. One possible way to reduce this would be to remove the influence of the lower limbs by completing the balance task in sitting, although whether this posture is sensitive enough to elicit change would need to be explored further (Bergquist et al., 2019).

6.5 Conclusions

In conclusion, this chapter has discussed the impact of FRED exercise on the static balance and dynamic movement control of working-age adults with LBP. There was a significant increase in mediolateral total sway path length in the bilateral eyes open condition, which strongly correlated with a reduction in pain intensity immediately post-intervention. This finding may indicate that six weeks of FRED exercise can reduce bracing and protected postures caused by LBP. There were no other significant findings in static balance in this study, which is in line with some other previous exercise intervention research. Movement variability, as an ersatz measure of FRED dynamic postural control, improved pre-and post-intervention, suggesting an element of task learning and postural control affecting the FRED progress. The average movement frequency reduced post-intervention, and this may be an appropriate target frequency for future studies. This chapter is the final one which considers six weeks of FRED intervention in an otherwise healthy community living adult population. There have been indications that FRED is a suitable tool for rehabilitation in chronic low back pain, and the reciprocal relationship with LBP and post-flight reconditioning suggest that FRED is also suitable for the astronaut population. Therefore, FRED research now needs to be undertaken in a higher-fidelity spaceflight simulation to assess the suitability of FRED as a post-flight rehabilitation tool.

7 Chapter 7 Participant reported pain before, during and after 60-days head-down bed rest.

Chapters four to six investigated FRED exercise in LBP patients. The LBP study was an initial step towards determining the effectiveness of FRED exercise for astronaut post-flight reconditioning. However, despite the similarities between LBP and post-flight deconditioning, a higher fidelity spaceflight analogue. Head-down tilt bed rest is considered a well-tolerated physiological model of microgravity off-loading and fluid shift (Green & Scott, 2018). The following three chapters will explore the influence of 13 days of FRED exercise plus standard reconditioning (FRED) or standard reconditioning alone (CON) following 60-days of HDT during the Artificial Gravity European Space Agency Bed rest (AGBRESA) study undertaken at :envihab DLR, Cologne, Germany. This chapter considers the effect of FRED exercise on patient-reported back pain associated with long-duration HDT bed rest.

7.1 Methods

The study was approved by the committee (2018143) of the North Rhine Medical Association (Ärztekammer Nordrhein) in Düsseldor, Germany, and was registered in the German Clinical Trials Register (DRKS-ID: DRKS00015677). The AGBRESA study is discussed in detail in chapter 3.3. Briefly, 24 participants (eight female) undertook 60-days of 6° head-down tilt (HDT) bed rest across two campaigns (C1: spring/summer; C2: autumn/winter), with 15-day baseline data collection (BDC) and 14-day recovery, periods pre- and post-bed rest, respectively. During the HDT phase, participants were assigned to either intermittent or continuous artificial gravity or control groups. During the recovery period, participants were then assigned using a balanced methodology to either the FRED exercise (FRED) or control groups (CON). All participants received an introduction to FRED before data collection during the BDC phase. The FRED group trained every day from R+1 to R+13 in the laboratory under supervision for safety reasons. Both the FRED and CON group received standard reconditioning, discussed in chapter 3.5.4. Two researchers (KL and EDM) collected all data except administering the pain questionnaires completed in the evening by study staff.

7.1.1 FRED intervention

Initially, it was unknown how physically deconditioned and affected by bed rest the participants would be. Therefore, a conservative approach was taken when planning the FRED training programme while staying in line with chapter 4.2.1, where total exercise time per participant = 177± 12minutes. As only total training time was moderately correlated to functional improvements, the AGBRESA study used increases in training time and increased crank size to progress the exercise and increase difficulty.

From the outset, it was clear that the participants were physically able and willing to train for longer than initially planned, even immediately post-bed rest. As the LBP Study suggested that total training time played a role in the effectiveness of FRED exercise (see chapter 5.4.1), it was decided to increase the planned training time to the maximum possible within the 30-minute timeslot available. In C1, each participant was offered the chance to do additional 'bonus' exercise intervals on top of the planned 3-minute training intervals. Most participants chose to undertake the extra training time from the first training session. When it became apparent that three-minute intervals were not providing a training challenge, and after discussion with the participants, it was decided that training intervals could be increased to four and then five minutes, leading to a 42% increase in total training time compared to the original plan.

Therefore, the C2 training plan was modified to provide a higher training load from the outset. A two-tier approach was taken; the original training plan was the lower minimum level and a higher C1-matched optimal level. This tiered structure allowed for any potential clinical needs in the C2 participants while maintaining the scientific rigour of the study. The new training plan equalled 258 minutes of exercise compared to the average achieved in C1 (253±18 minutes). Campaign 2 participants completed 255±9 minutes of FRED exercise. Table 7.1 shows the pre-study protocol compared to the modified C2 training plan for comparison.

Table 7-1 A comparison of exercise time planned before the study, and for C2 to balance the increased time completed during C1

	Planned pre-study		**Actual-C2**	
Study Day	**Exercise pattern**	**Total exercise time (minutes)**	**Exercise pattern**	**Total exercise time (minutes)**
R+1	3 x 2 min	6	4 x 2 min	8
R+2	5 x 2 min	10	6 x 2 min	12
R+3	4x 3 min	12	4x 3 min	12
R+4	5x 3 min	15	5x 3 min	15
R+5	5x 3 min	15	4 x 4min	16
R+6	5x 3 min	15	5 x 4min	20
R+7	5x 3 min	15	5 x 5 min	25
R+8	5x 3 min	15	5 x 5 min	25
R+9	5x 3 min	15	5 x 5 min	25
R+10	5x 3 min	15	5 x 5 min	25
R+11	5x 3 min	15	5 x 5 min	25
R+12	5x 3 min	15	5 x 5 min	25
R+13	5x 3 min	15	5 x 5 min	25
Total		**178**		**258**

7.1.2 Pain Questionnaires

Bespoke pain questionnaires with a body chart, Visual Analogue Scale (VAS) and subjective questions about pain duration, nature, and quality, were administered during BDC (BDC-12 and BDC-1), weekly during HDT (HDT7, HDT14 etc.), each day during the first week of the recovery phase (R+1 to R+7) and on the penultimate recovery day (R+12), as shown in Figure 7.1. An example pain questionnaire is shown in appendix C. Questionnaires were provided in German and were administered by the AGBRESA study nursing team in the evening at around 2130. The questionnaire was developed with a research team from Charitè University, Berlin. Due to a scaling issue when printed, the VAS line was 9.2cm long. Therefore, a correction factor was applied during the analysis.

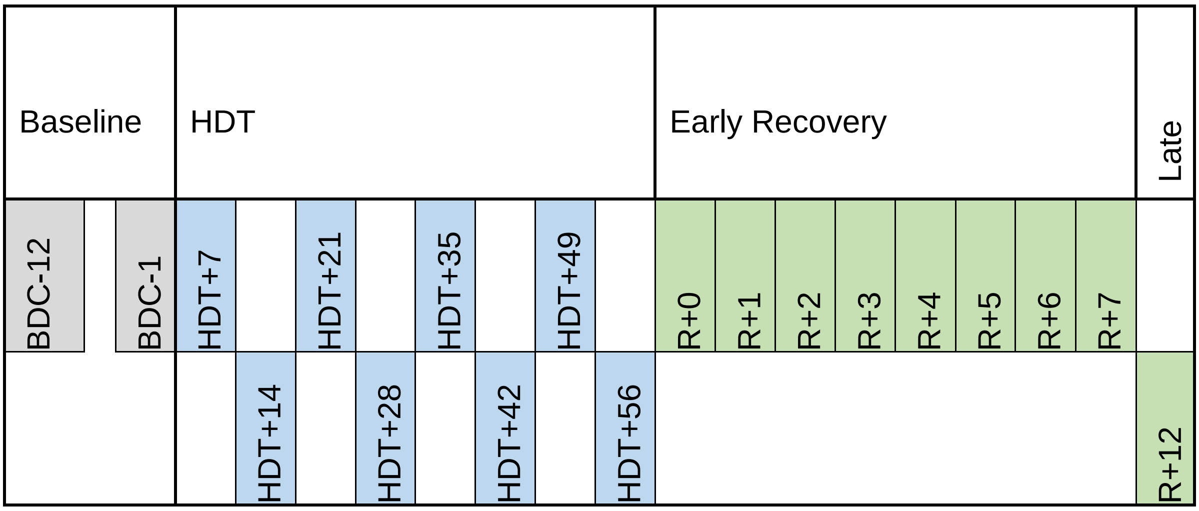


Figure 7-1 Time points for questionnaires throughout the AGBRESA study.

7.1.1 Pain Questionnaire analysis

Pain questionnaire data were analysed by one researcher (KL). The VAS was measured manually using electronic callipers to provide a comparison reference. It was then measured electronically using the Adobe Acrobat Reader DC (Abode Inc, 2017) tool for PDF using the internal calibration in millimeters and 0.01mm precision. The interrater ICC (2,1) = 0.919 for the VAS score and 0.996 for the area, showing an excellent agreement between days. The Acrobat measurement tools were also used to measure the pain area for each body chart. The number of pain reports was calculated by counting how many individual back pain reports each participant provided per day. If the participant shaded two or more pain areas but gave one written report explaining both, it was counted as one pain report. However, if a participant shaded two or more pain areas and provided an individual written report for both, they were counted as separate pain reports. Therefore, each participant could provide more than one back pain report per day.

7.1.2 Complications and deviations from the planned protocol

In the original AGBRESA protocol, the two groups of 12 participants should have completed either a summer or winter campaign. C1 was completed without incident;

however, C2 lost one participant before starting the campaign due to a broken leg and then a further three during BDC due to medical issues. Because of the unusually high drop-out rate, DLR decided to recruit four new participants (C2+), who started data collection three weeks after the main C2 group. Due to logistical issues, C2+ had a condensed BDC. Initially, C2+ had 3 CON and 1 FRED participant; however, due to the need for the research team to stay in Germany for additional time, this was changed on request to all members being in the CON group.

7.1.3 Participant Challenges

During the FRED familiarisation training, four different team members delivered the FRED introduction due to logistical issues. To try to ensure the same information was delivered to all participants, guidance notes and training were given to all team members delivering the training. A standardised safety briefing was also given to all participants before the start of each testing session which covered foot placement, mounting and dismounting FRED, and the instructions "move as slow and steady as possible, keep nice and controlled" and to move "like a snail on crutches". During the warm-up phase of testing (initial 3 minutes), the participant repeatedly went out of the FRED variability area. They were advised on how to perform better, such as foot placement, leg loading and posture. However, if they could perform adequately without input, no advice was given; this was to reduce the bias offered by participant coachability.

7.1.4 Injuries

Several injuries occurred throughout the recovery period, although only one participant officially had to reduce their training time because of it. Issues included

4x patella pain, 2x tendinopathy at the ankle, back strain, intramuscular haematoma (calf), 2x neuropathies related to the biopsy site, and one traumatic calcaneus bursitis; the participants affected are shown in Table 7.3. Participants had access to medical staff throughout the study. The FRED R+13 data collection was cancelled for participant A because of their ankle pain and reduced range of movement due to heavy strapping. Table 7-2 Participant injuries were reported to the research team during the AGBRESA study.

Table 7-3 Participant ID and injury details for all participants

Participant ID	MSK issue
A	Ankle injury
G	Back injury
K	Patella pain
T	Haematoma
R1	Patella pain
Q1	Patella pain
U	Ankle Tendinopathy
W	Biopsy neuropathy
Y	Calcaneus bursitis
Z	Biopsy neuropathy

7.1.5 FRED exercise deviations

Two main confounding factors affected the participant’s ability to undertake FRED exercise; the injuries noted above and interactions with other experiments. These impacted the participant’s ability and willingness to undertake exercise. In C1, one training session was cancelled (G, session 2) due to acute back pain following a maximum voluntary contraction exercise, and one episode of back ‘pressure’ without pain (L, session 10) was reported during FRED session was completed as planned. In C2, two FRED sessions were cancelled: one due to a left gastrocnemius haematoma pain (T, session 2) and another (participant U, session 12) due to bilateral oedema pain. Participants X, session 10 and W, session 10, were shortened due to time constraints, and the lost exercise time was added to the next session. Due to a mechanical breakdown on FRED, participants J, K, L, P, and V completed at least one training session on a backup exercise device (FREDa); otherwise, all sessions were completed on the primary FRED.

7.1.6 Statistical Analysis

Pain questionnaire results are given as mean ± standard deviation, other than the number of pain areas given as a sum of reports. Statistics were calculated on an intention to treat, and analyses were carried out using SPSS 26 (IBM Corp. Released 2018. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). All data were treated as non-parametric after failing a Shapiro-Wilks test. A Kruskal Wallis test was carried out, followed by a post hoc Mann Whitney U test if significance was indicated. A $p = 0.05$ was used for significance. Cohen's d effect sizes were calculated using Microsoft Excel 2016 with thresholds for size as Cohen (1988) defined.

7.2 Results

7.2.1 Number of back pain reports by study day

Because of missing data, it was not possible to use an intention to treat approach with pain duration; therefore, only effect size is reported. Specific time points were chosen to represent the baseline (BDC-12 and BDC-1) very early post-re-ambulation (R+1, after one FRED session and one massage/ stretching session), the midway point of reconditioning (R+6, six FRED sessions, three reconditioning sessions and three physio sessions completed), and the very end of reconditioning (R+12). R+1 was chosen rather than R+0 to minimise the acute effects of returning to an upright posture, coupled with the heavy experiment load and very long testing day, typically between 0700 and 2100 on R+0. There were comparable pain reports between groups on R+1, with 13 in the control group and nine in the FRED group. On R+6, the FRED group showed a marked improvement with only three back pain reports compared to 12 in the CON group. By the end of the reconditioning period, both groups reported three instances of back pain. These results suggest FRED is more effective at reducing pain than conventional reconditioning alone in the early reconditioning phase, but that the efficacy diminishes over time. This is shown in figure 7.3.

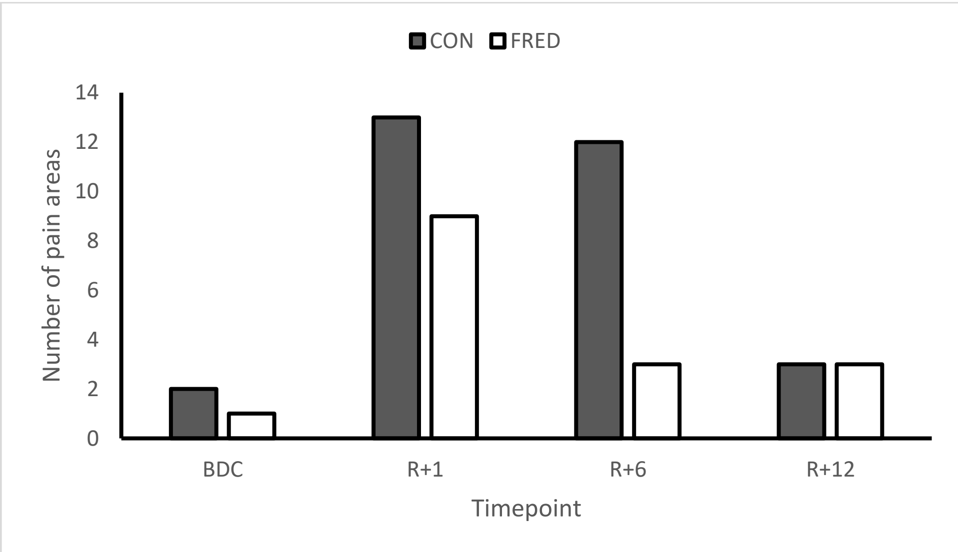


Figure 7-2 Number of back pain reports by study day in the baseline period (14 days), very early (R+1), early (R+6) and Late (R+12) reconditioning stage

7.2.2 Pain Intensity

The VAS was measured in millimeters. A Kruskal Wallis test showed no significant difference between the FRED and CON groups at any time point, shown in table 7.3.

Table 7-4 shows the Kruskal Wallis test results for each time point which showed no significant difference in pain intensity between the FRED and CON groups

Time Point	Degrees of freedom	H	significance
BDC	1	0.494	0.482
R+1	1	0.331	0.565
R+6	1	0.059	0.807
R+12	1	0.494	0.331

Both groups experienced an increase in pain between BDC and R+1, with a very large effect size in each group (Cohen,1988) (Figure 7.3, Table 7.5). The FRED group reported less pain intensity on R+1 (28.2±12.2mm) than the CON group (44.6±22.1mm) following one FRED session. Both groups reported comparable amounts of pain intensity at R+6 (FRED = 15.4±5.5mm and CON = 14.8±7.2mm). The FRED group then reported low levels of pain for the rest of the reconditioning period, while the CON group reported an increase in pain by the end of the study (FRED = 14±6mm and CON = 39.7±6.1). However, this had a small effect size.

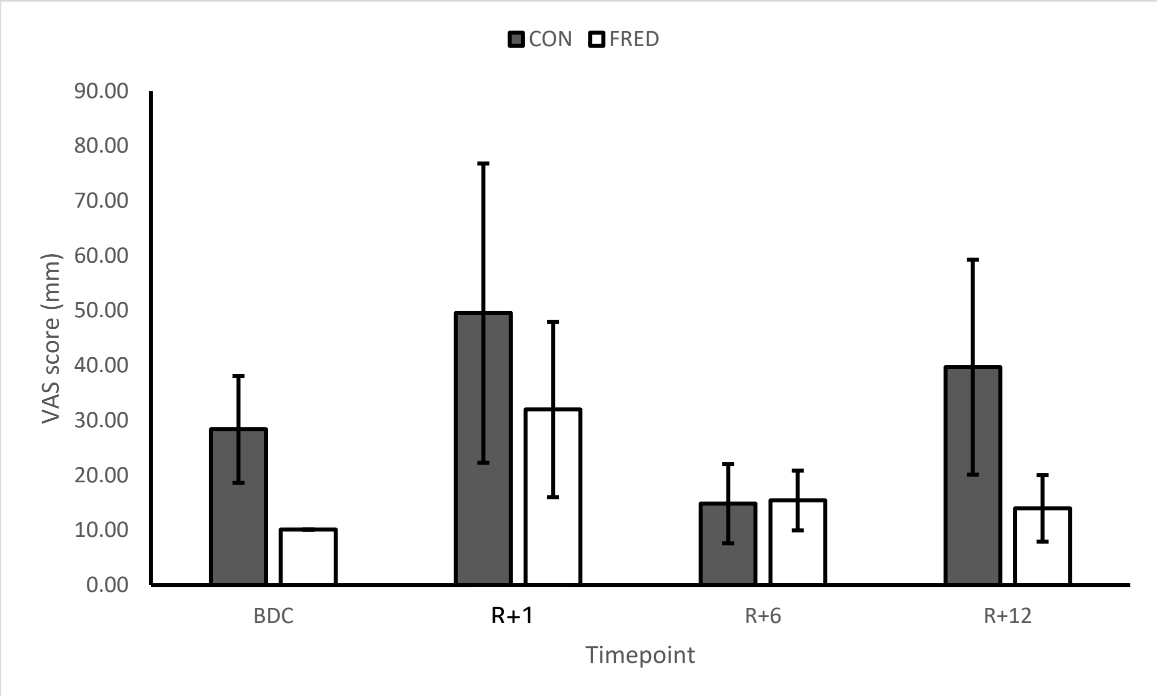


Figure 7-3 shows the VAS mean ±SD scores comparison between CON (grey) and FRED groups white)

Table 7-5 Visual Analogue Scale (VAS) confidence interval and effect size

VAS		Confidence Interval		
condition	Δ mean	lower	upper	Effect Size
FRED BDC to R+1	18.111	14.319	21.903	**2.70**
FRED R+1 to R+6	-12.825	-18.160	-7.490	**-1.36**
FRED R+6 to R+12	-1.420	-4.681	1.841	-0.25
CON BDC to R+1	16.212	7.210	25.214	**1.14**
CON R+1 to R+6	-29.748	-38.045	-21.451	**-0.87**
CON R+6 to R+12	24.883	17.293	32.473	-0.11

7.2.3 Pain Area

Pain area (mm^2) was not significantly different between the FRED and CON groups, with the Kruskal Wallis test results shown in table 7.6.

Table 7-6 shows the Kruskal Wallis test results for each time point which showed no significant difference in pain area between the FRED and CON groups

Time Point	**Degrees of freedom**	**H**	**significance**
BDC	1	0.363	0.574
R+1	1	0.22	0.883
R+6	1	0.253	0.615
R+12	1	0.324	0.569

Despite the lack of significant difference, there was a very large effect size in the FRED group between R+1 and R+6, shown in table 7.5. Pain area is the only measure in which FRED did more poorly than the CON group. The CON group average area at R+1 was 70.4± 28.3mm^2, compared to 117.7±96.7mm^2 in the FRED group. The FRED group showed very large levels of individual variability compared to the CON group. By R+6, both groups showed a reduction in pain area (CON = 70.7±33 and FRED = 84.1±48.1mm^2), which showed a larger effect size for the FRED group. By R+12, CON had a smaller area than FRED (37±41.1 mm^2 and 69.6±41 $mm^{2,}$ respectively).

Table 7-5. shows the pain area confidence intervals and effect sizes, where there is a large effect size between FRED and CON at R+6 and R+12

		Confidence Interval		
Condition	**Δ mean**	**lower**	**upper**	**effect size**
FRED BDC to R+1	94.342	67.056	121.628	0.29
FRED R+1 to R+6	13.700	-27.199	54.599	**1.55**
FRED R+6 to R+12	-14.708	-39.960	10.545	**-1.49**
CON BDC to R+1	33.333	17.327	49.339	0.31
CON R+1 to R+6	47.323	29.994	64.652	0.19
CON R+6 to R+12	-33.498	-46.179	-20.817	-0.33

7.2.4 Maximum Pain Duration

Maximum pain duration was assessed because of anecdotal evidence from the LBP study. Because of missing data, it was not possible to take an intention to treat approach to the pain duration data; therefore, it was not possible to carry out inferential statistics. R+1 data were comparable between both groups (FRED = 6.4±3.1hr and CON = 8.1±4.8hr); however, by R+6, the FRED group symptom duration was around one-third of the CON group (2.7±0.5hr and 9.5±5hr respectively), this was maintained for the FRED group at R+12 (2.5±1.9hr), and the CON group had also reduced to a similar level (3.3±1.9hr). This is shown in table 7.6 and figure7.5.

Table 7-7 shows the maximum pain duration for the FRED and CON groups. Both groups show a large effect size after pre-post HDT and between R+1 and R+6.

condition	Δ mean	Confidence Interval lower	upper	effect size
FRED BDC to R+1	5.929	5.062	6.795	**3.87**
FRED R+1 to R+6	-3.762	-4.762	-2.762	**-1.42**
FRED R+6 to R+12	-0.167	-0.829	0.496	-0.14
CON BDC to R+1	6.136	4.208	8.064	**1.74**
CON R+1 to R+6	1.364	-1.420	4.147	**-1.50**
CON R+6 to R+12	-6.167	-7.941	-4.392	-0.05

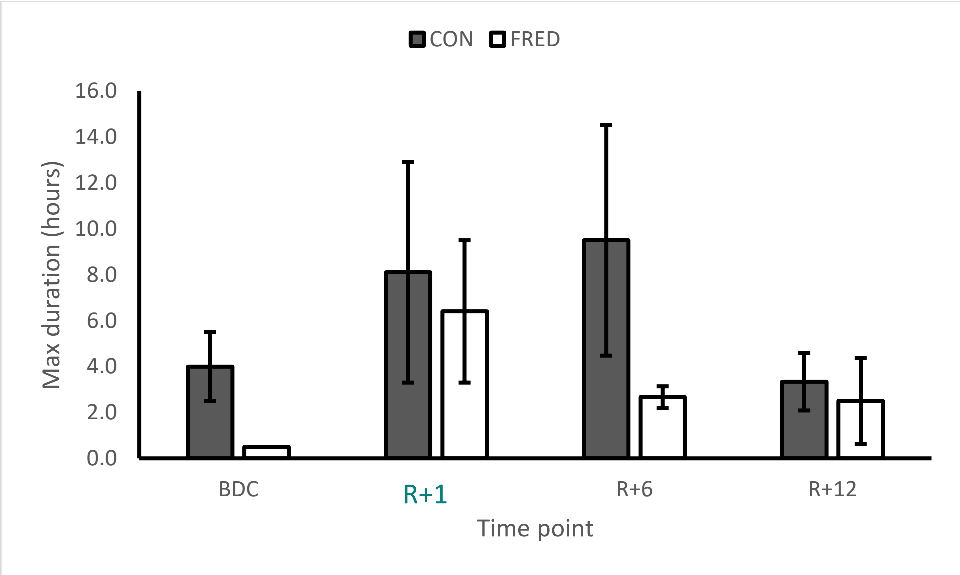


Figure 7-4. shows maximum pain duration comparison for the FRED and CON group, which is large at R+6 before equalising at R+12.

7.3 Discussion

The main findings of this chapter were that FRED exercise is more effective in the early intervention period than standard reconditioning alone at reducing back pain intensity, maximum symptom duration and number of pain reports, although these changes failed to reach significance where tested. Overall, the number of pain reports in the AGBRESA study were higher than those reported in previous studies.

Pain area on a body chart was the only metric in which the FRED group did less favourably than the CON group.

7.3.1 Number of Pain reports

This study found that by R+6, the FRED group reported fewer back pain instances than the CON group, with nine and 13 reports, respectively. To date, very few studies have explored LBP during long-duration bed rest. Rittweger et al. (2006) undertook a 56-day horizontal bed rest study with 20 male participants. They reported that both the intervention and control groups experienced a total of four LBP episodes during bed rest and a total of seven episodes during the two-week recovery phase, which is notably lower than the more than 200 reports from the current study. The differences in numbers could be due to how the data were collected and analysed in both studies, for example, questionnaire frequency and definition of pain report. Pain intensity was not reported in the study; therefore, pain severity and its potential impact cannot be assessed. Miokovic et al. (2014) considered lower limb pain in the 2nd Berlin bed rest study, finding a higher incidence of pain episodes upon re-ambulation than bed rest. This increase agrees with the current findings. In the AGBRESA study, 78% of back pain reports were recorded during the recovery phase (171/205 reports), and 96% (165/171 reports) of those were in the first seven days of recovery. This finding has clinical implications for both astronauts and hospitalised populations for whom bed rest is a necessary treatment. For example, some women with pregnancy complications (Shibayama et al., 2016) may need additional support in the early re-ambulation period, such as pain management.

7.3.2 Pain Intensity on a VAS score

Pain measured on the VAS was approximately 18mm less in the FRED group at R+1 after one FRED session (FRED = 28.2±12.7mm, CON = 44.6±22.1mm). This is a clinically important difference, as determined by Hägg et al. (2003). This difference may have been due to the FRED activity providing low-level exercise-induced analgesia, possibly via the release of endogenous opioids (Hviid et al., 2019). Haviid et al. (2019) found the six-minute walk test was sufficient to have a measurable exercise-induced analgesic effect on pain tolerance in a healthy population, which is around the length of a single FRED exercise bin in the current study. Another possibility is that the extra time in an upright posture decreased pain intensity due to improved posture, blood flow or tissue loading. This hypothesis is supported by the fact that the FRED group did not report any pain in the coccyx (FRED = 0 reports and CON = 13 reports) and less pain in the gluteal regions (FRED = 17 reports and CON = 25 reports), which are areas which might be expected to be uncomfortable with prolonged sitting/ inactivity (Lirette et al., 2014). The additional social interaction with the FRED team may also positively affect pain perception (Klaber Moffett & Richardson, 1997). VAS scores were the same for both groups at R+6 (FRED = 15.4±5.5mm and CON = 14.8±7.2mm). The FRED group remained around this level at R+12 (14±6.1mm), but the CON group increased pain intensity to 37.1±6.1mm. This result suggests that FRED exercise has a hypoalgesia effect which continues for the duration of the study. Although Hoffman et al. (2004) determined that the minimal exercise threshold for exercise-induced analgesia was 75% VO_2max for more than 30 minutes, there is some evidence that lower-intensity exercise may also have a pain modulating effect (Hviid et al., 2019). Overall, our understanding of the effect of exercise on pain perception is still in its infancy and requires further research in human participants (Sluka et al., 2018); therefore, further research on the effect of FRED on pain modulation is needed before firm conclusions can be drawn.

Head-down tilt bed rest was initially conceived in this experiment as a model of chronic non-specific low back pain, as bed rest has previously been shown to induce muscular deconditioning, which presents similarly to that seen in chronic low back pain (Hides et al., 2016). However, in this study, back pain was most commonly reported following high-intensity experiments such as MARES, drop-down box test and reconditioning, not the inactivity of bed rest, which goes against current research into the causes of low back pain episodes (Suri et al., 2018). Pain reporting during bed rest was low, with only 21% of pain questionnaire test days reporting back pain (31 reports/144 questionnaire days). Therefore, bed rest may more accurately model acute or acute on chronic low back pain. Further research is needed to confirm this and consider FRED's role in the treatment of acute back pain. It is also important to note that back pain was not experienced in isolation. Pain downstream in the kinetic chain in the lower limb and feet were also widely reported (Table 7.6); however, further analysis of this data was omitted as the data were collected as part of a study by Charitié University. The presence of wide-spread pain in other areas may have led to the participant’s central nervous system becoming more sensitised and susceptible to back pain (Graven-Nielsen & Arendt-Nielsen, 2010)

Table 7-8 total number of pain reports in considering the entire body split into the whole back (C-spine to S-spine) and any area outside of the back

	BDC		Recovery	
	Non-Back	Whole Back	Non-Back	Whole back
CON	15	5	258	154
FRED	15	1	209	96

7.3.3 Pain Area on a body chart

Analysis of the body chart as a representative pain drawing showed this was the only parameter measured in which the FRED group did less favourably than the CON group, consistently experiencing larger areas of pain than controls. Two participants (L and J) reported extensive pain areas (>500mm^2), which were at least twice the size of other participants, an example of which is shown in figure 7.4.

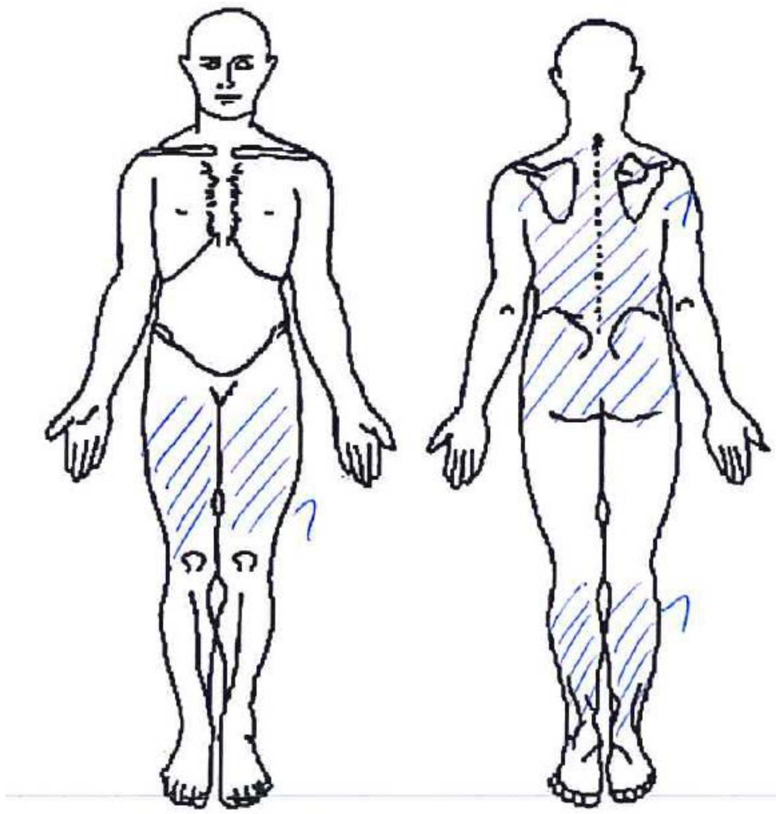


Figure 7-5. Figure 7.4 shows an example of a widespread pain area covering the entire back from participant J on day R+2

The larger areas of pain reported in the FRED group may have been down to the increased physical activity of undertaking FRED exercise, which included extra walking between the habitation module and laboratory and standing for extended periods while undertaking FRED exercise. Caution must be taken when considering pain area because the quality of the pain drawings in this study varied significantly by participant, with some shading an area as requested during the familiarisation session and some circling areas. This inconsistency introduced a high level of variability in the quality of data available for analysis. One potential improvement for future research would be using an electronic body chart for pain drawings that have been shown to have excellent test-retest reliability in chronic low back pain (Barbero et al., 2015).

7.3.4 Maximum pain duration

FRED exercise's ability to influence pain symptom duration was suggested by the anecdotal evidence collected during LBP. In the AGBRESA study, it was confirmed that FRED exercise does have a positive effect on symptom duration. Maximum pain duration was around 7 hours less in the FRED group (FRED = 2.7±0.5hr, CON = 9.5± 4hr) at R+6. This was maintained in the FRED group until the end of the study. By R+12, both FRED and CON groups experienced around 2.5±1.9 and 3.3±1.9 hours, respectively. This suggests that FRED exercise had a positive influence in the early reconditioning phase but that the added benefit of FRED exercise on top of standard rehabilitation reduces over time. From a medical operational perspective, this suggests that FRED could be utilised as an acute rehabilitation tool in the first six days after landing in post-flight crewmembers, as fewer hours of pain may facilitate improved wellbeing and physiological outcomes in other areas.

7.3.5 Limitations

One limitation affecting the measurement of pain data were the language barrier experienced between the researchers and participants. All participants were German-speaking, while the primary FRED team were English-speaking, meaning that humour, idiomatic language, and cultural references were sometimes lost. All experiment instructions were provided in written English and German; however, most participants chose not to read the instructions provided and preferred spoken instructions. This limitation was particularly apparent in C1 when all the FRED team members spoke English, and one participant required a translator, who was a member of the DLR team. The need for a simultaneous translator means that the nuances of information given to the participant may have been lost. This issue was addressed in C2 and C2+ when a German-speaking FRED team member was available for all data collection days. The bed rest environment and closed nature of the study may have negatively affected some participants. Anecdotal observation suggested that discussing pain or low mood in the company of other participants led to further reports of pain; this is called the Ripple Effect (Barsade, 2002). This observation may be confirmed by the finding that out of eleven participants reporting pain during HDT, eight belonged to a research pair, one had no partner, and two had partners who did not report pain. A research pair shares a start day and timetable and therefore had more time together than other participants, so they may be more likely to pass on their pain. The pain reports were unlikely to be linked to specific experiments as they were scattered throughout the study with no visible clustering effect. Future research may need to consider the psychosocial complexity of working in an enclosed environment with a small group and how these may affect any physiological measures collected.

7.4 Conclusion

This chapter has discussed participant-reported pain intensity, duration, location, and area and provided methodological details for the AGRESA study. In addition to standard rehabilitation, FRED exercise leads to reduced pain intensity, the number of pain reports and pain duration and symptom distribution compared to conventional rehabilitation alone in the early reconditioning period (R+1 to R+6). However, it may also increase the area in which symptoms are experienced. Overall, pain has not been widely studied in the non-clinical bed rest population, and future research is needed to elucidate how the complex interplay of psychosocial and physiological factors experienced in this environment affect pain and pain perception. The next chapter will consider how changes in the lumbopelvic muscles, specifically Lumbar Multifidus and Transversus Abdominis, are affected during the reconditioning process following bed rest using Magnetic resonance imaging and ultrasound imaging.

8 Chapter 8: Ultrasound and MRI in bed rest

Chapter 7 highlighted the effects of FRED intervention on patient-reported pain, which suggested that using FRED was beneficial in the early post-HDT, the potential structural changes that may explain this will be explored further. This chapter will explore the structural changes in the lumbopelvic muscles to determine the magnitude of deconditioning resulting from 60 days of head-down tilt bed rest and whether 13 days of FRED exercise could ameliorate those changes in addition to the standard DLR post-bed rest rehabilitation protocol.

8.1 Methods

A detailed methodology is given for the ultrasound imaging (USI) technique in chapter 3.4.1.1 and MRI in section 3.4.1.3. Briefly, USI Images were collected at rest, at 100% maximum voluntary contraction (MVC) and approximately 30% MVC during an abdominal drawing-in manoeuvre (ADIM). Data were collected during the baseline data collection (BDC-4) before bed rest, the last day of head-down tilt (HDT59) and at the end of the recovery period (R +13). A repeated-measures ANOVA was conducted to compare the effect of time and group on the TrA muscle thickness during bed rest (BDC-4 to HDT59) and recovery (HDT59 to R+13). All images were collected at the end-expiration of normal tidal breathing by one researcher (KL). The technical team from the German Aerospace Institute (DLR) collected the MRI data using a T1 weighted DIXON-VIPE sequence in a supine head-down tilt. The machine is shown in figure 8.1. MRI was collected on BDC -4, R+0 R +13, and was taken in the horizontal position after at least 30 minutes of lying supine. Ultrasound images were not collected at R+0 because of scheduling conflicts with other experiments. Therefore, images were collected on the last day of head-down tilt (HDT60). To account for this position, all images were collected in the 6° head-down tilt position. Results are given as mean ± standard deviation unless stated. Measurements were taken on the left and right sides of the body and analysed separately to determine if the lateral preference noted in the LBP study was also present in the AGBRESA data. Lumbar Multifidus cross-sectional area (LM CSA) at the L5/S1 level between time points R+0 and R+13. De Martino et al. (in publication) confirmed a decrease in LM CSA due to deconditioning following-60-day HDT in this participant group, and so has been excluded from this analysis. A repeated-measures ANOVA was conducted to compare the effect of time, group and side on L5/S1 LM CSA after 13 days of FRED reconditioning in addition to normal DLR reconditioning (FRED group), or FRED control (CON group) with DLR reconditioning alone.

Figure 8-1 A participant being prepared for the MRI. They are secured with a lower-body restraint to minimise movement artefact. This image was taken from outside the MRI room to minimise disruption and potential interaction with the magnetic field.

8.1.1 Protocol Deviations and complications

The complexity and time constraints of the whole AGBRESA study led to several protocol deviations in the FRED team segment. The standard ADIM instructions led to the mainly German-speaking participants completing an abdominal crunch rather than drawing the stomach towards the spine. The instructions 'imagine pulling your belly button towards your spine' was altered slightly to 'be as tall and thin as possible while drawing your belly button towards your spine, which produced better results in this population. A list of other protocol deviations is given in Table 8.1. All planned images were collected.

Table 8-1 protocol deviations for USI for all AGBRESA participants

Day	Participant	Deviation
BDC	G	Hands behind head for imaging due to comfort (no pillow)
BDC	L	USI collected by EDM as KL was ill
R+0	D	All testing cancelled due to cardiovascular instability, re-tested on R+1
HDT59	H	Breath-holding during imaging? - unable to confirm
HDT59	J	Breath-holding during imaging
HDT59	M	Unusual imaging noted, with bucket handle motion of ribs during respiration and no visible EO at rest, EO was visible at 100% MVC
BDC	Q1	Participant presented with inverted images; i.e. usually, hyperechoic lines were black in images.
BDC	R1	Tiny participant, non-standard transducer placement used to capture images
R+13	T	Breath-holding during 100% MVC
R+13	U	EDM collected R 100% MVC as KL was unable to get a clear image

There were also instances of knee pillows not being used; this was due to time pressures or participants not transferring onto the plinth, as they were moved in their beds at HDT59, sometimes with blankets in situ. This did not affect the image quality, and no participants complained of being uncomfortable throughout the imaging process. Details of FRED training, training deviations and injuries are given in chapter 7.1.1.

8.1.2 Statistical Analysis

After assumption testing, the imaging data were treated as normally distributed parametric data. A repeated-measures ANOVA with post hoc Bonferroni correction was carried out using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). A p = 0.05 was used for significance. Cohen's d Effect sizes were calculated using Microsoft Excel 2016 with thresholds for size as Cohen (1988) defined.

8.2 Results

8.2.1 Lumbar Multifidus cross-sectional area data via MRI

There was a statistically significant effect of group, Wilks' Lambda = 0.36, F (1,11) = 19.7, p = 0.00 (Table 8.2).

Table 8-2 shows LM CSA repeated measures ANOVA results for CSA change between R+0 and R+13.

Effect	**Wilks' Lambda**	**F**	**F (hyp, error)**	**Sig.**
GROUP	0.36	19.70	1,11	**0.00**
SIDE	0.88	1.55	1,11	0.24
TIME	0.79	2.97	1,11	0.11
GROUP * TIME	0.94	0.72	1,11	0.41

The effect size was minimal in the CON group and small in the FRED group; this can be seen in table 8.3.

Condition	Mean Difference	95% Confidence Interval for Difference		Effect Size
		Lower Bound	Upper Bound	
CON Right	0.37	-0.69	2.49	0.13
CON Left	0.24	-0.63	2.28	0.08
FRED Right	0.67	-0.74	2.68	0.20
FRED Left	0.79	-0.69	2.49	0.22

Figure 8-2 descriptive statistics for the L5/S1 LM CSA.

The CON group gained 0.37cm^2 ± 1.30 cm^2 on the right and 0.24 cm^2 ±1.37 cm^2 on the left. The FRED group gained 0.67cm^2 ± 1.77cm^2 on the right and 0.79cm^2 ± 1.71cm^2 on the left. Although the mean difference in FRED LM CSA was around twice that seen in the CON group, not all participants responded to the FRED intervention and individual variability was high. Comparisons of both the absolute change and relative change in LM CSA is shown in Figures 8.3 and 8.4, respectively.

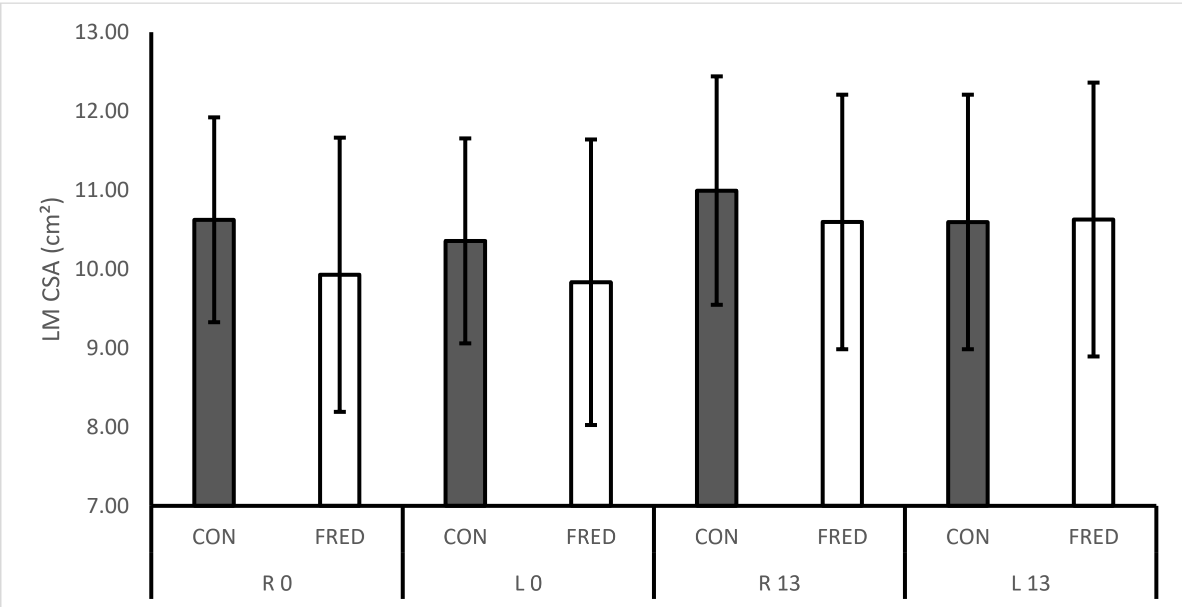


Figure 8-3 Absolute change for L5/S1 LM CSA for the FRED (white) and CON (grey) groups at R+0 and R+13 for the left and right sides.

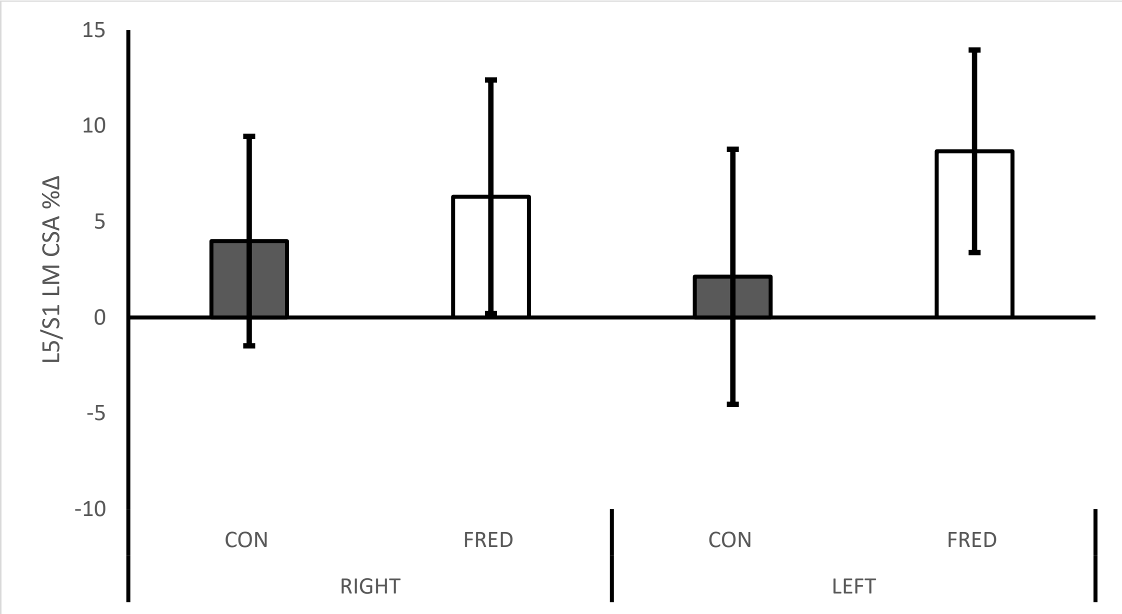


Figure 8-4 Percentage change in L5/S1 LM CSA The FRED group had an average increase of 8.4±5% on the left and 6.3±5.11% on the right. The CON group had an average of 2.5±6.2%on on the left and 4.1±5.6% on the right.

8.2.2 Transversus Abdominis Thickness via Ultrasound.

There were no statistically significant results for any time or group interaction (Table 8.3), although the CON group did show a reduction in size with a small effect size at rest between BDC and HTD59 (Table 8.4; Figure 8.5).

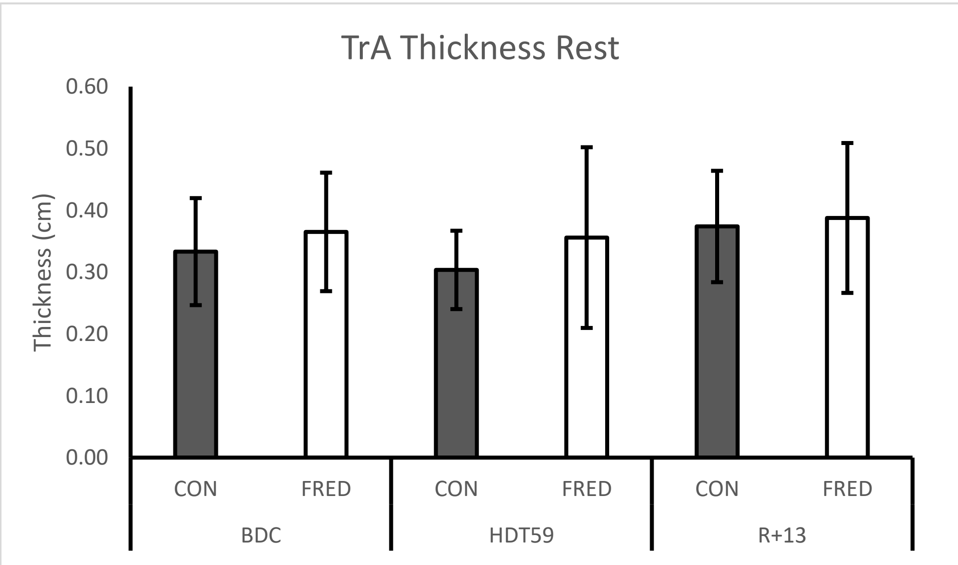


Figure 8-5 `TrA thickness at rest for the FRED and CON groups, showing a slight loss of thickness in the CON group between BDC and HDT59

Table 8-3 TrA repeated measure AVOVA results

Condition	Effect	Wilks Lambda	F	F (hyp, error)	Sig.
Rest	GROUP	0.84	2.10	1,11	0.18
	TIME	0.75	1.63	2,10	0.24
	GROUP * TIME	0.96	0.20	2,10	0.82
100% MVC	GROUP	0.80	2.69	1,11	0.13
	TIME	0.95	0.24	2,10	0.79
	GROUP * TIME	0.82	1.12	2,10	0.36
30% MVC	GROUP	0.88	1.56	1,11	0.24
	TIME	0.91	0.49	2,20	0.62
	GROUP * TIME	1.00	0.01	2,20	1.00

Table 8-4. shows the confidence interval and effect size for the TrA muscle thickness changes in the FRED and CON group.

Condition				Mean Difference	95% Confidence Interval		Effect Size
					Lower Bound	Upper Bound	
LEFT	HDT59 to R+13	Rest	CON	0.07	0.15	0.53	0.46
			FRED	-0.03	0.16	0.58	-0.12
		100% MVC	CON	-0.02	0.24	0.86	-0.07
			FRED	0.02	0.26	0.95	0.07
		30% MVC	CON	0.0	0.19	0.67	0.00
			FRED	0.0	0.20	0.74	-0.01
RIGHT	HDT59 to R+13	Rest	CON	-0.03	0.04	0.14	-0.20
			FRED	-0.02	0.03	0.12	0.16
		100 % MVC	CON	0.04	0.08	0.28	0.12
			FRED	-0.01	0.08	0.27	0.22
		30% MVC	CON	-0.04	0.07	0.26	-0.14
			FRED	-0.03	0.06	0.23	0.22

8.3 Discussion

The main finding of this study was that there was a statistically significant group effect on LM CSA. Transversus abdominis showed no statistically significant effect of FRED exercise for any parameter.

8.3.1 Lumbar Multifidus

During the reconditioning phase, up to 30 minutes of FRED exercise plus standard reconditioning for 13 sessions significantly increased LM CSA compared to standard reconditioning alone, although both groups show an increase in Multifidus size. This finding disagrees with Hides et al. (2011), who found that general exercise and Motor Control Training were equally effective at restoring LM CSA after 60 days of HDT. However, unlike the current lab-based exercise intervention where all participants had their FRED sessions supervised, in the BBR2 study, participants received either 30 minutes of general exercise or MTC between R+2 and R+7, followed by seven days of home exercise program. LM CSA was measured by MRI on R+14; therefore, direct comparison is difficult because the home exercise compliance was not monitored.

8.3.2 LM CSA and Pain In HDT

As the bed rest study offered a unique opportunity to study the interactions between pain and muscle architectural changes, a sub-analysis was carried out to determine if the two phenomena were linked. Participants were divided into those who reported at least one episode of back pain from T1 to the gluteal fold if the pain area extended into the lower spinal area. The thoracic spine was included because pain areas often traversed the thoracic, lumbar, and sacral regions. Any pain reported in the upper thoracic and cervical regions only were excluded. In total, there were 31 reports of back pain during HDT; 13 were excluded due to pain location, and of the remaining 18 pain reports, the Lumbar Multifidus cross-sectional area at the L5 /S1 was divided into participants reporting pain in HDT (N = 11) and those with no back pain reports (N = 13). A repeated-measures ANOVA with Bonferroni correction was carried out as detailed in Section 8.1.2. There was no statistically significant difference between participants reporting pain and those not reporting pain. The magnitude of deconditioning was the same in both groups. Both groups showed some improvements in CSA by R+13; this is shown in figure 8.5. Because the pain group started LM CSA around 1cm^2 smaller than the no-pain group, relative change was also assessed, shown in figure 8.6. These findings support the conclusion of Harrison et al. (2018), which suggest that in-flight pain and spinal deconditioning are not temporally linked and that post-flight deconditioning is a factor of spinal offloading, not pain inhibition.

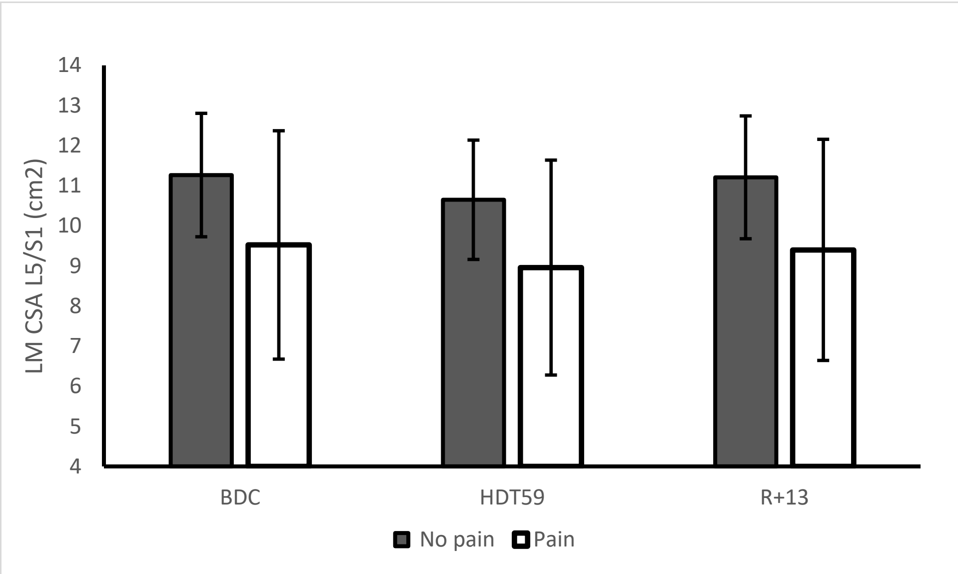


Figure 8-6 Absolute change in LM CSA at L5/S1 for participants who reported at least one episode of LBP during HDT compared to those who did not report any LBP.

The lack of difference between the pain-reporting and the no-pain group is interesting because it suggests pain was not a precursor to deconditioning in this sample. Participants experienced discrete, short, pain episodes much like SABP (Kerstman et al., 2012; Pool-Goudzwaard et al., 2015) rather than chronic long-duration pain exposure, e.g. Van Tulder et al. (1997). This suggests SABP has little effect on lumbopelvic muscle atrophy experienced after spaceflight, which disagrees with Hides et al. (2019), who suggested that astronauts experiencing space adaptation back pain may experience pain induced muscle inhibition leading to atrophy upon return to Earth. However, the findings of the pre-post-flight astronaut study by Harrison et al. (2018) do not support this.

It appears that bed rest, and by extension, spaceflight, can model lumbopelvic muscle atrophy and deconditioning, but not the effects of chronic pain. Longer-duration experimentally induced pain, such as that used by De Martino et al. (2019), may be a better model for future research in chronic non-specific LBP, which focuses on the physical effects of pain.

This finding that pain experienced during HDT is not a sign of deconditioning is particularly important from a spaceflight medical operational perspective because it suggests that astronauts and the healthcare professionals need to be aware that spinal deconditioning is silent, and that pain may not act as either a warning or preventative measure limiting overloading and overuse. In situations where deconditioning can reasonably be expected to have occurred, such as post-flight, it may be more operationally effective to assume that any load-bearing activity has the potential risk of harm regardless of symptomology. It may also be necessary for astronauts to routinely undertake pre-and post-flight monitoring, such as MRI or USI, to ensure that spinal deconditioning has resolved before returning to not only flight duties but also higher-risk activities of daily living.

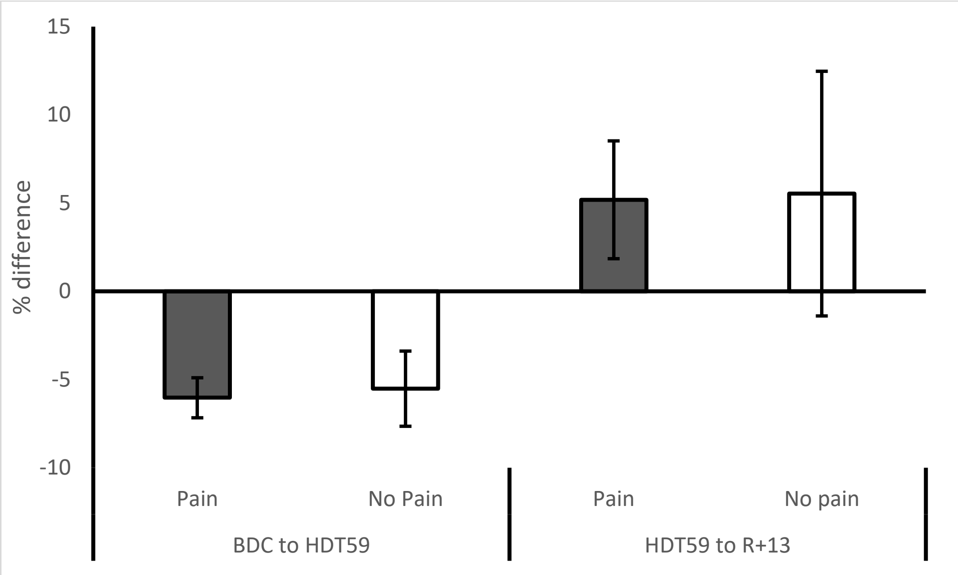


Figure 8-7 Relative difference in LM CSA shows that both the pain-reporting and no-pain group = behaved the same in respect to LM CSA changes throughout the AGBRESA study.

An example of an astronaut potentially returning to a high-risk activity early post-flight is shown in the Tweet below. David Saint-Jacques, of the Canadian Space Agency, spent 206 days in space on Expedition 58/59. On the 30th of June 2019, he Tweeted a picture of himself carrying his young daughter on his shoulders, a mere six days after landing, with the caption “An important milestone in my re-adaptation to gravity…” (Figure 8.6). Carrying a load, such a small child is an activity with a high spinal load (Chow et al., 2011). It requires good spinal control, stability, and strength (Panjabi, 1992), which without sufficient recovery time, may increase the risk of spinal injury (Chow et al., 2011). Astronauts need to be aware that they are at a potentially high risk of spinal injury, even if they feel normal after their return to Earth and experience no back pain.

Figure 8-8 shows a tweet sent by Astronaut David Saint-Jacques six days after landing from Expedition 58/59 and 206 days in space.

There is also a low (Mukaka, 2012) correlation ($r = 0.42$) between average LM CSA change and total exercise time, with a moderate ($r = 0.62$) relationship on the left and a low negative correlation in the right ($r = -0.47$), which suggests that FRED may have a specific benefit for the left-hand-side despite the lack of a significant difference between sides in the CSA. Due to the small number of FRED participants, further research is needed to confirm the correlation between total exercise time and LM cross-sectional area.

8.3.3 Transversus Abdominis

To date, less is known about the effects of HDT on Transversus Abdominis (TrA), although Belavy et al. (2017) found an 18% decrease in thickness after 60 days, and spaceflight experience suggests that TrA is also at risk of atrophy (Hides et al., 2016). The current study disagrees with previous findings and did not find that bed rest significantly affected TrA thickness. Therefore, a sub-analysis was carried out to determine why the result differed from the previous study. No research was found which looked at the post-bed rest recovery period, only exercise intervention during the HDT phase.

Participants were divided into artificial gravity intervention (n = 8 per group) of either a control group (CTRL), who received no intervention, continuous artificial gravity (cAG) who received 30 minutes of centrifugation a day or intermittent artificial gravity group (iAG) who received 6x5 minutes of centrifugation per day. As shown in Figure 8.8, the CTRL group behaved as expected (Belavý et al., 2017), losing 17.5±18.4.%. The cAG group experienced a smaller loss at 11.9± 21%, and the iAG gained 2.5±17.5 TrA thickness during HDT (Figure 8.8). One potential reason for the results seen was the use of an anti-gravity straining manoeuvre (AGSM) to counteract the deleterious effects of acceleration. An AGSM involves bracing the abdominal muscles while performing a Valsalva manoeuvre for several seconds (Gradwell & Rainford, 2016). This tensing of the abdominal wall may have mitigated TrA deconditioning in this experiment. The iAG group performed multiple AGSM per session as the centrifuge accelerated to its working load. Repeated activation of TrA in this group seems to have had a protective or even hypertrophic effect on TrA. The cAG group performed fewer AGSM, as the centrifuge only accelerated once per session; however, this does appear to have mitigated some of the muscle loss during HDT. During the recovery phase, the cAG group experienced the most recovery (31±15.9%), followed by the iAG group (17.3 ±5.3%), with the CTRL group showing the least recovery (14.±17.3%).

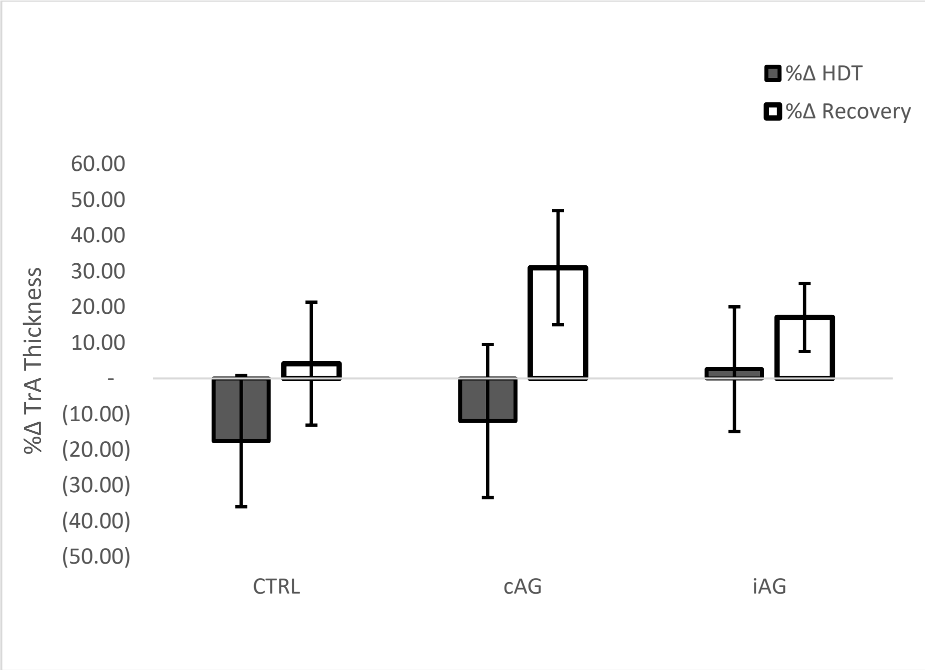


Figure 8-9 TrA thickness change as a percentage in each AG group during HDT and recovery phases. N = 8/ group

A further sub-analysis was then completed to determine the combined effect of FRED exercise and artificial gravity. In the CTRL group, FRED intervention appears to have had no additional benefit compared to standard rehabilitation alone; however, in the iAG group, FRED does appear to have found a minimal additional benefit. However, the group sizes were small (n = 4), and individual variability was high; therefore, this finding needs to be treated cautiously. While the groups were too small to complete inferential statistics, the data suggest that previous exposure to artificial gravity impacts the effectiveness of FRED intervention (Table 8.4; Figure 8.9). It is unknown why the CTRL/FRED group showed minimal recovery during the reconditioning phase. It seems unlikely, considering the positive interactions seen in other outcomes, which are discussed in this and other chapters, that FRED has an inhibitory effect on muscle growth for most individuals. However, two participants (F and J) in the CTRL/FRED group, one in the CTRL/CON group (Z) and one participant (N) in the iAG/CON group showed a negative response to exercise, losing muscle mass in both the LM and TrA muscles during the recovery period. It is important to note that all participants completed standard reconditioning. Therefore, the negative response during the recovery period was to multiple types of exercise interventions, not FRED alone. This has an important implication for future long-duration planetary exploration missions. Pre-mission screening may be required to ensure crewmembers have an expected and appropriate response to the available exercise countermeasures. This idea is supported by Kukoba et al. (2019), who found some repeat-long-duration-flyers have positive responses to bungee and ARED exercise on bone mineral density, while some do not, suggesting some crewmembers respond better to specific countermeasures. Future research needs to explore the predictive factors which can identify individuals who would not benefit from exercise countermeasures.

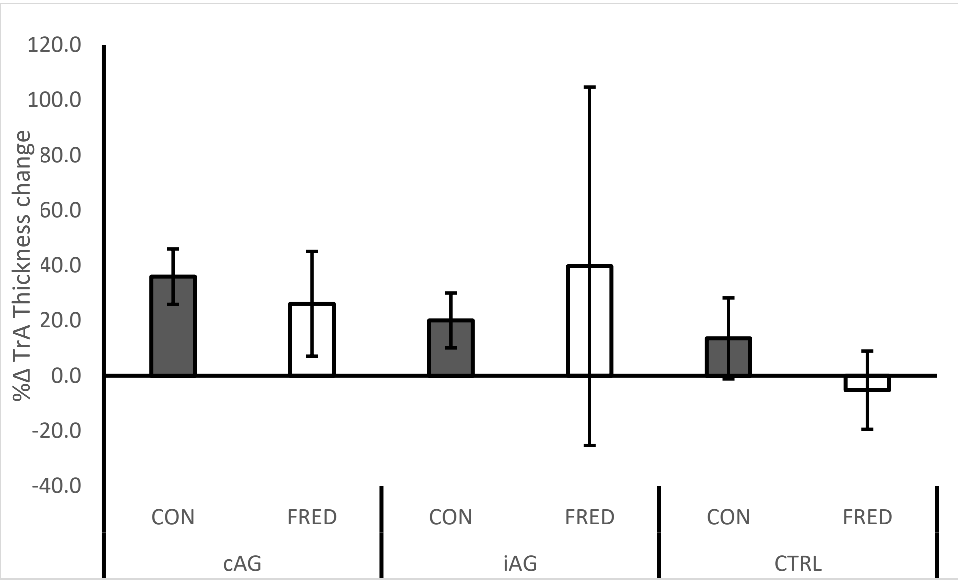


Figure 8-10 Percentage change for TrA thickness during recovery, divided by AG and exercise intervention. N = 4/ group

8.3.4 Limitations

The main limitation of this study was the need to use ultrasound imaging instead of high-resolution MRI for the TrA due to respiration movement artefact in the Dixon-

VIPE sequence. Ultrasound imaging was challenging in this study because of the 6° head-down tilt position. The tilted position moved the viscera in the cephalic direction, meaning the TrA was not in the standard anatomical position compared to previous research in other populations or the second Berlin bed rest study, where images were taken supine. While this visceral movement was accounted for by completing all USI in a head-down position, the lack of change seen in TrA may be caused by positional abdominal distension. Participants also received ultrasound imaging at different times of the day, some immediately after meals, which may also have affected abdominal positioning and the presence of gas bubbles within the image.

In some cases, abdominal massage was required to move gas bubbles out of the imaging area. The abdominal movement caused by respiration was controlled by collecting images at end-expiration. However, some participants held their breath during data collection; this was exacerbated by the language barrier between the participants and the research team, preventing data collection instructions from being correctly understood. This limitation was particularly evident at the C1 baseline data collection, which was discussed more fully in Chapter 7.

One factor that makes interpreting HDT data difficult is the varying environmental factors between studies: the AGBRESA study does not include the use of pillows throughout the entire experiment, which altered the participant's bed rest position compared to previous studies of lumbopelvic musculature, such as the BBR2, which allow both pillows and more upper body movement (Belavy et al., 2010b). While a completely flat posture potentially provided a more accurate model of spaceflight offloading by minimising neck and trunk flexion, comparisons to previous bed-rest studies are limited by the alteration in bed rest environment. Further limiting the ability to analyse and compare data are the need for sub-analysis of tiny groups due to the complex nature of the bed rest intervention.

8.4 Conclusion

This chapter has discussed the effects of FRED intervention on the Lumbar Multifidus cross-sectional area and Transversus Abdominis muscle thickness following 13 days of reconditioning after long-duration bed rest. Thirteen sessions of FRED exercise plus standard reconditioning led to a statistically significant increase in LM CSA. This finding suggests that FRED could be a suitable reconditioning tool in post-flight astronauts who experience spinal muscle deconditioning. In contrast to previous research, this study did not find a statistically significant effect of bed rest, or FRED exercise, on the Transversus Abdominis muscle thickness. This finding may be due to the anti-gravity countermeasure and related use of the anti-G straining manoeuvre, which at least partially mitigated bed rest related deconditioning in the TrA muscle. A crucial operational finding is that back pain during HDT was not linked to Lumbar Multifidus deconditioning; the pain was not a precursor, or warning, of LM deconditioning; therefore, participants/ crewmembers may not know they are in a deconditioned state and be at higher risk of injury. The examination of structural changes of the spinal antigravity muscles alone is not enough to truly understand the effectiveness of FRED. Due to the importance of these muscles in the maintenance of upright posture, the next chapter will examine the effectiveness of postural control in both static balance and dynamic movement variability following bed rest and reconditioning.

9 Chapter 9: Static Balance and Dynamic movement Control after Bed Rest

Chapter 8 highlighted the effects of FRED intervention on cross-sectional area and thickness changes in Lumbar Multifidus (LM) and Transversus Abdominis (TrA) using ultrasound and MRI. This chapter will explore the possible neuromuscular control changes in static balance and dynamic movement control following FRED reconditioning.

9.1 Methods

A detailed methodology for the static balance and dynamic movement control tasks are given in Chapter 3.4.2The participants stood so that the force plate x-direction and the body x-direction were aligned, as shown in Figure 9.1. Data were collected in each balance condition for 60 seconds or until a loss of balance occurred, whichever came sooner. Test postures included bilateral standing on a firm surface, single-leg standing on a firm surface (right), and bilateral standing on a compliant surface. All postures were completed with eyes open, and eyes closed.

Table 9-1 Balance task abbreviations and conditions.

Abbreviation	Condition
BEO	Bilateral Eyes open (firm surface)
BEC	Bilateral eyes closed (firm surface)
BEO_Foam	Bilateral Eyes Open (foam pad)
BEC_Foam	Bilateral eyes Closed on (foam pad)
	Single-Leg stand (not included in the analysis)

Changes in dynamic movement control were assessed by measuring mean FRED movement variability over one minute as an indirect measure of neuromuscular control, with better control indicated by smaller variability in the rotational frequency of the footplates. The FRED movement variability task is described in detail in Chapter 3.4.3. It consisted of four minutes of FRED exercise, of which the first three minutes were a warm-up and normalisation period, and the final minute consisted of data collection.

Balance and FRED movement variability data were collected at BDC-4, R+0 and R +13. Because of the potential for falls or loss of balance, especially during the R+0 data collection, a light handhold was provided before starting data collection at all time points. Participants had the opportunity to rest between postures if required.

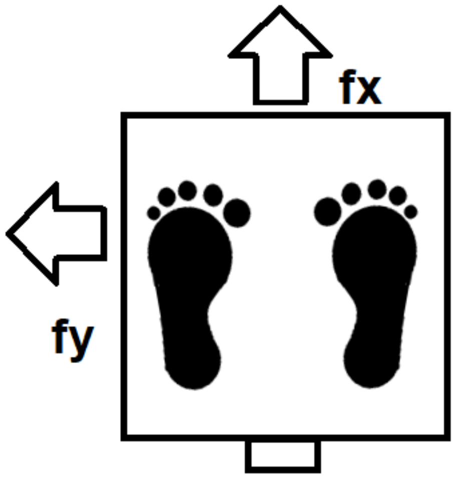


Figure 9-1 shows the anatomical and force plate directions in this experiment. Participants were positioned so that the force plate x-direction and body x-direction were aligned.

9.1.1 Complications and variations from planned protocol

As noted in Chapter 8, participant D completed the data collection at R+1 due to cardiovascular instability at R+0. Participants C, D, F, G, and Hall wore compression stockings during R+0 testing. Participant U wore compression stockings at the R +13 data collection at the medical team's request. The training intervention was the same as described in Chapter 7.2.1, consisting of up to 30 minutes of FRED exercise for 13 days between R+1 and R+13.

9.1.2 Statistical analysis

After assumption testing, the static balance data were treated as normally distributed parametric data. A repeated-measures ANOVA with a post hoc

Bonferroni correction was carried out using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). p=0.05 was used for significance. Cohen's, d, Effect sizes were calculated using Microsoft Excel 2016 with thresholds for size as Cohen (1988) defined. Total sway path length (TSPL) in both the anteroposterior (A-P) and mediolateral (M-L) directions were analysed for each of the six balance conditions. Single leg stance was excluded from the statistical analysis due to the high level of data loss, as participants were unable to complete the required 60 seconds of data collection at all data collection time points.

9.2 Results

Results are given as mean ± standard deviation unless stated otherwise. The abbreviations used for the balance tasks are given in Table 9.1.

9.2.1 Static Balance

A repeated-measures ANOVA with a Bonferroni correction showed a significant main effect of time for all balance conditions (Table 9.2) and no main effect of group for any balance condition. It also showed that they were a significant interaction effect between group*time in every balance condition.

Table 9-2 Repeated Measures ANOVA with Bonferroni correction results for each balance task and sway direction. There was a significant effect of time and group*time, but not group alone.

	Effect	Value	F	Hypothesis df	Error df	Sig.
BEO A-P	time	0.288	12.381b	2	10	**0.002**
	group	0.935	.759b	1	11	0.402
	time * group	0.19	21.303b	2	10	**0.001**
BEO M-L	time	0.528	4.462b	2	10	**0.041**
	group	0.988	.136b	1	11	0.719
	time * group	0.254	14.721b	2	10	**0.001**
BEC A-P	time	0.216	18.138b	2	10	**0.00**
	group	0.967	.374b	1	11	0.553
	time * group	0.298	11.767b	2	10	**0.002**
BEC M-L	time	0.362	8.830b	2	10	**0.006**
	group	0.984	.181b	1	11	0.679
	time * group	0.346	9.459b	2	10	**0.005**
BEO foam A-P	time	0.32	10.609b	2	10	**0.003**
	group	0.856	1.843b	1	11	0.202
	time * group	0.441	6.338b	2	10	**0.017**
BEO_foam M-L	time	0.327	10.310b	2	10	**0.004**
	group	0.995	.053b	1	11	0.823
	time * group	0.195	20.591b	2	10	**0.001**
BEC_foam A-P	time	0.321	10.565b	2	10	**0.003**
	group	0.828	2.283b	1	11	0.159
	time * group	0.467	5.707b	2	10	**0.022**
BEC_foam M-L	time	0.54	4.257b	2	10	**0.046**
	group	0.964	.412b	1	11	0.534
	time * group	0.17	24.446b	2	10	**0.001**

9.2.1.1 Bilateral Eyes Open (BEO)

Figure 9.2 shows the total sway path length in the A-P direction for both FRED and CON groups at BDC, R+0 and R+13. Total sway path length increased significantly between BDC and R+0 for both FRED (p = 0.004; d = 1.9) and CON (p = 0.010; d = 1.8) groups. A significant reduction in total sway path length were observed between R+0 and R+13 for FRED (p = 0.006) and CON (p = 0.021) groups, with large effect sizes in both groups, d = -1.2 and d = -1.5 for FRED and CON groups, respectively. No significant differences were seen between BDC and R+13 for either the FRED (p = 0.810; d = 0.5) or CON (p = 0.104; d = 0.4) groups.

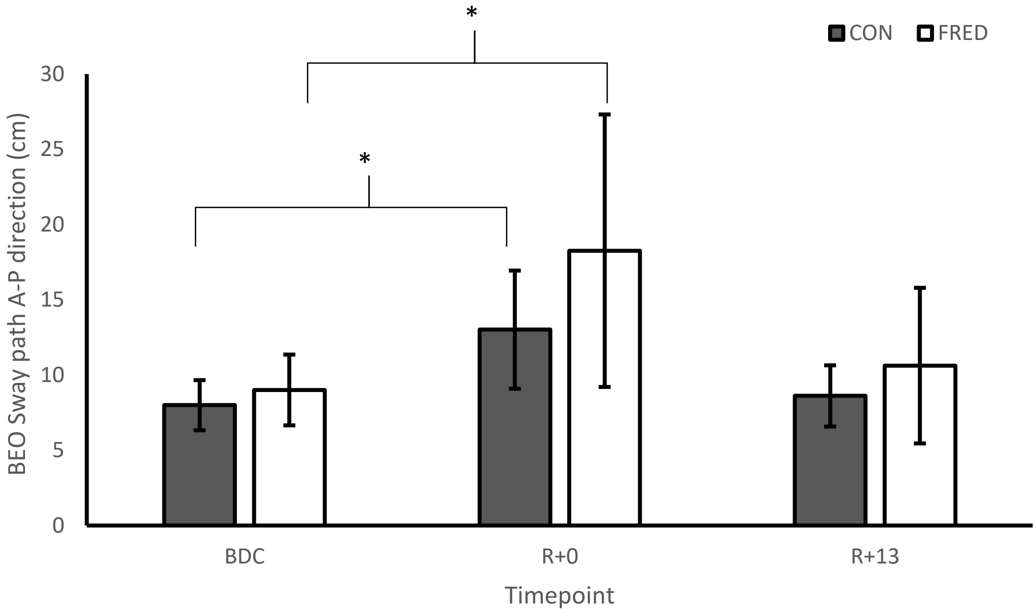


Figure 9-2 Total sway path length is shown for the bilateral eyes open condition in the A-P direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.05.

Figure 9.3 shows the total sway path length in the BEO M-L direction for both FRED and CON groups at BDC, R+0 and R+13. Significant changes with very large effect size were seen between BDC and R+0 for the FRED (p = 0.012; d = 1.5) and CON (p = 0.031; d = 1.5) groups. Sway path length significantly reduced between R+0 and R+13 for CON (p = 0.026), but not for the FRED group (p = 0.067) However, reductions with large effect sizes were seen in both groups (FRED: d = -1.0; CON: d = -1.5. No significant differences were seen between BDC and R+13 for either the FRED (p = 0.383; d = 0.2) or CON (p = 0.715; d = -0.3) groups.

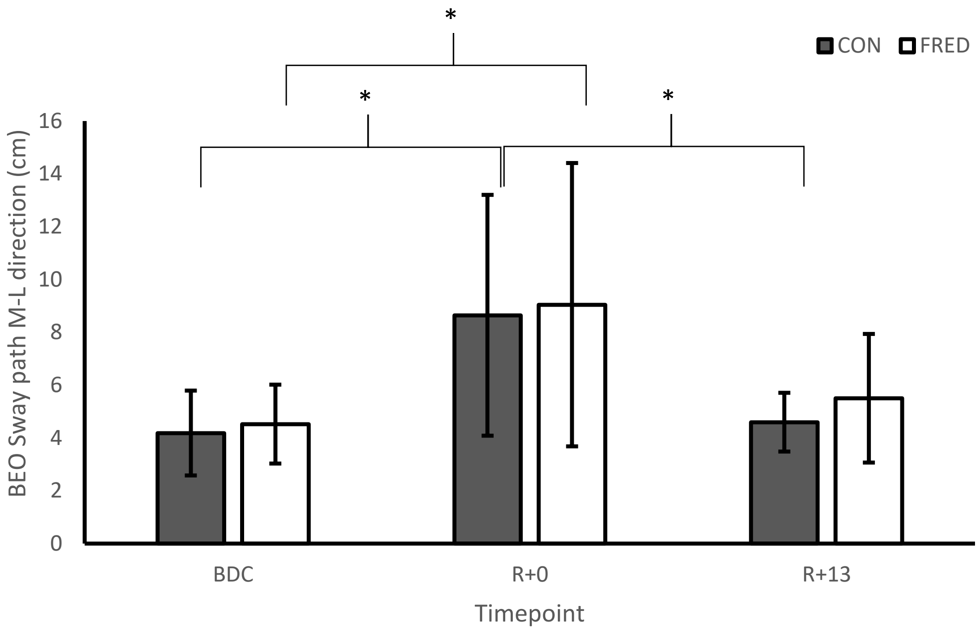


Figure 9-3 Total sway path length is shown for the bilateral eyes open condition in the M-L direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * Indicates significant differences between time points at $p<0.05$.

9.2.1.2 Bilateral Eyes Closed (BEC)

Figure 9.4 shows the BEC total sway path length in the A-P direction for both groups. There were significant increases between BDC and R+0 for FRED (p=0.048, d =1.6) and CON (p=0.002, d =2.0) groups. There were significant decreases, although with very large effect sizes, between R+0 and R+13 in both groups (FRED: p = 0.021, d = 1.4; CON: p = 0.006, d = -1.6). There were no significant changes between BDC and R+13 in either the FRED (p = 0.810, d = 0.3) or CON (p = 0.104, d = 0.6) group.

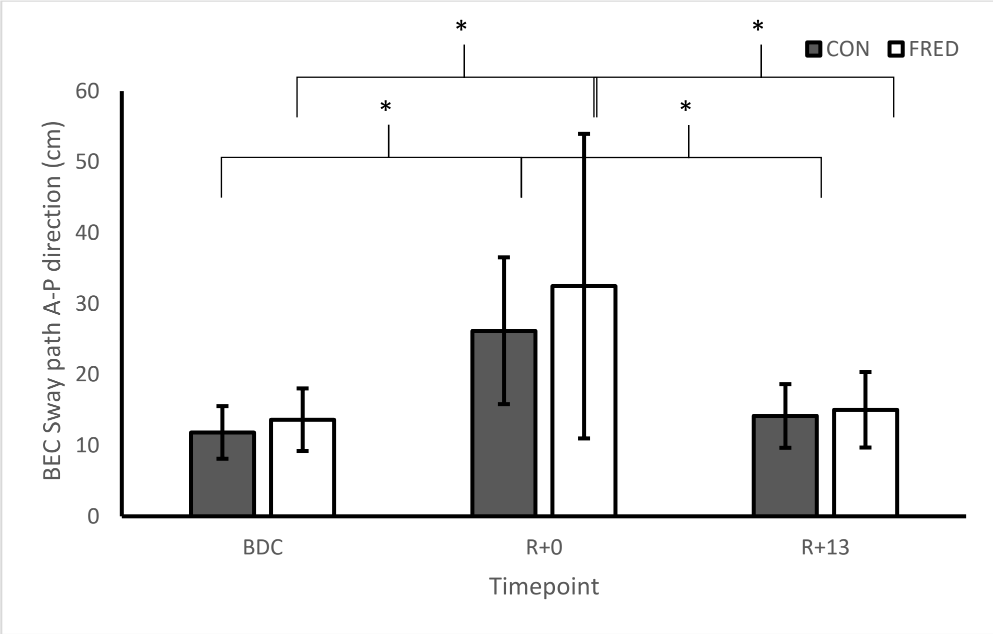


Figure 9-4 Total sway path length is shown for the bilateral eyes closed condition in the A-P direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.05

Figure 9.5 shows the total sway path length for the BEC condition in the M-L direction for the FRED and CON groups. Between BDC and R+0 there was a significant increase in sway path length with a very large effect size in both FRED (p = 0.003, d = 1.7) and CON (p = 0.26, d = 1.4) groups. Between R+0 and R+13 there was a significant reduction in sway path length in both FRED (p = 0.004, d = -1.7) and CON (p = 0.026, d = -1.5) groups, with very large effect sizes in both groups. There was no significant change between BDC and R+13 in either group with small effect sizes (FRED: p = 1.000, d = -0.2; CON: p = 1.000, d = 0.1).

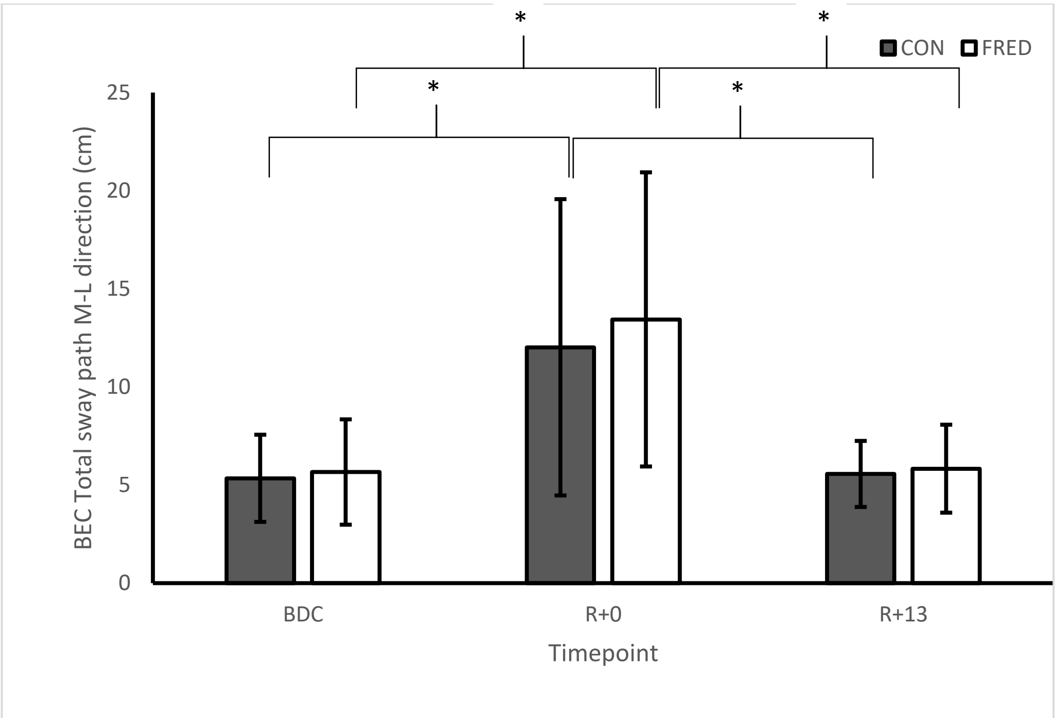


Figure 9-5 Total sway path length is shown for the bilateral eyes closed condition in the M-L direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.

9.2.1.3 **Bilateral Eyes Open_foam (BEO_foam)**

Figure 9.6 shows the BEO_foam total sway path length in the A-P direction. Between BDC and R+0 the FRED group showed a significant increase in path length with a very large effect size (p = 0.006, d = 1.2), whilst the CON group showed a non-significant change with a large effect size (p=0.114, d =0.8). A significant decrease was seen between R+0 and R+13 in the FRED group (p = 0.004, d = -1.6), although the CON group did not show a significant change (p=0.154, d = -1.1). Both groups showed no significant difference between BDC and R+13 (FRED: p = 0.555, d = 0.5; CON: p = 1.000, d = -0.5).

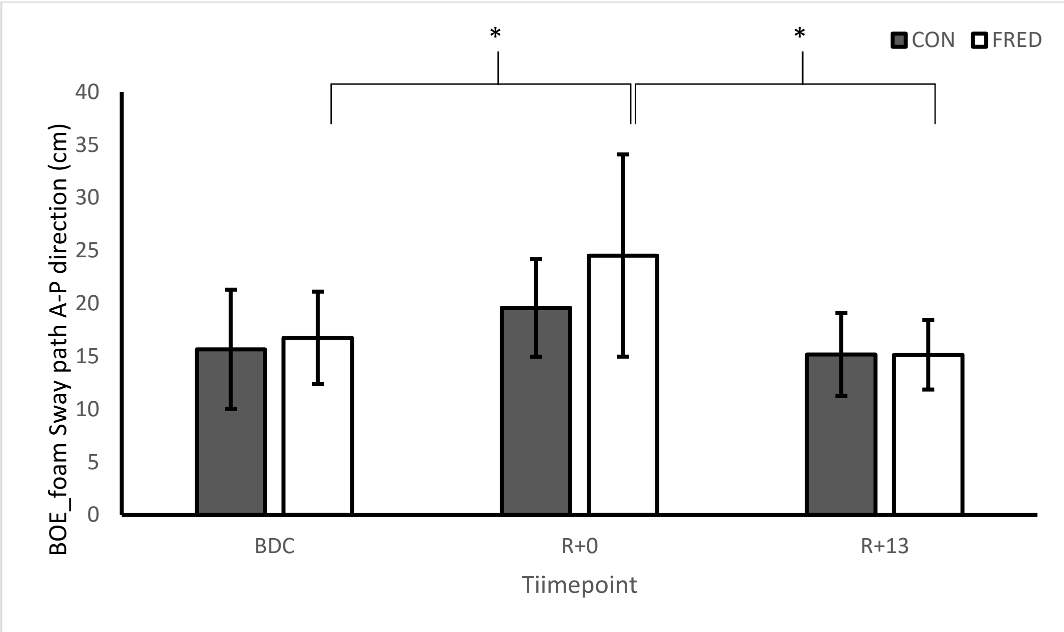


Figure 9-6 Total sway path length is shown for the bilateral eyes open foam condition in the A-P direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.05

Figure 9.7 shows the BOE_foam condition in the M-L direction. Between BDC and R+0 the FRED (p = 0.008, d = 1.5) and CON (p = 0.004, d = 1.5) groups had significant increases in sway path length, with very large effect sizes. Between R+0 and R+13, with a significant decrease in sway path length in both groups (FRED: p = 0.006, d = -1.4; CON: p = 0.003, d = -2.1), with a larger effect size in the CON group. There was no significant difference in either group between BDC and R+13 with a medium effect size in the FRED group and trivial effect in the CON group (FRED: p=0.701, d = 0.5; CON: p = 0.645, d = 0.1).

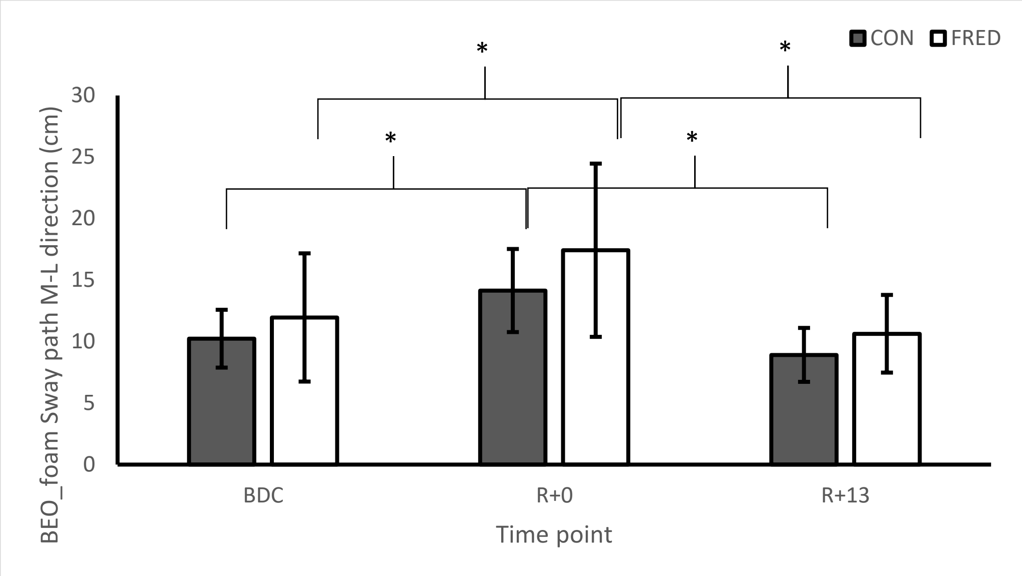


Figure 9-79-3 Total sway path length is shown for the bilateral eyes open foam condition in the M-L direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.05

9.2.1.4 Bilateral Eyes Closed_foam (BEC_foam)

Figure 9.8 shows the BEC_foam in the A-P direction for the FRED and CON groups. Between BDC and R+0 the FRED group showed a significant increase in sway path length with a trivial effect size (p = 0.018, d = 1.3), while the CON group did not show a significant change (p = 0.414, d = 1.5). Between R+0 and R+13 the FRED group significantly reduced (p = 0.001, d = -1.7). The CON group did not show a significant change, although there was a medium effect size (p = 0.124, d = -0.7). There was no significant difference between BDC and R+13 in either group (FRED: p = 0.293, d = -0.5; CON: p = 0.997, d = 0.1).

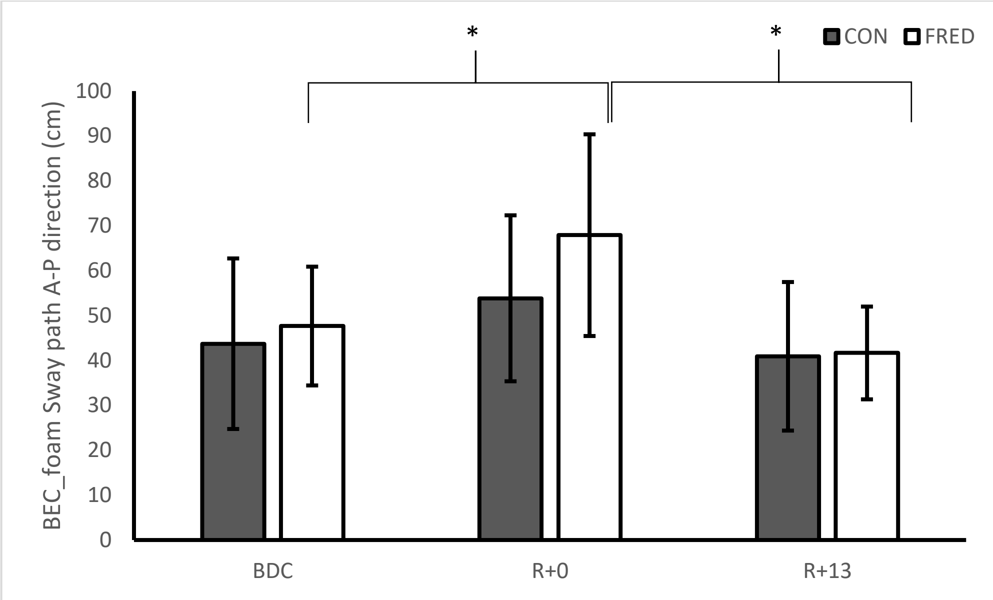


Figure 9-8 Total sway path length is shown for the bilateral eyes closed foam condition in the A-P direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.05

Figure 9.10 shows the BEC_foam condition in the M-L direction for the FRED and CON groups. Between BDC and R+0, the FRED group showed a significant increase in sway path length (p = 0.001, d = 1.8), while the CON group did not significantly change but did have a large effect size (p = 0.169, d = 1.0). Between R+0 and R+13, both groups had a significant reduction in sway path length with large effect sizes (FRED: p = 0.002, d = 1.9; CON: p = 0.007, d = 1.9). The CON group showed a significant difference between BDC and R+13 with a medium effect size (p = 0.037, d = -0.6), while the FRED group did not show a significant change with a small effect size (p = 1.000, d = -0.2).

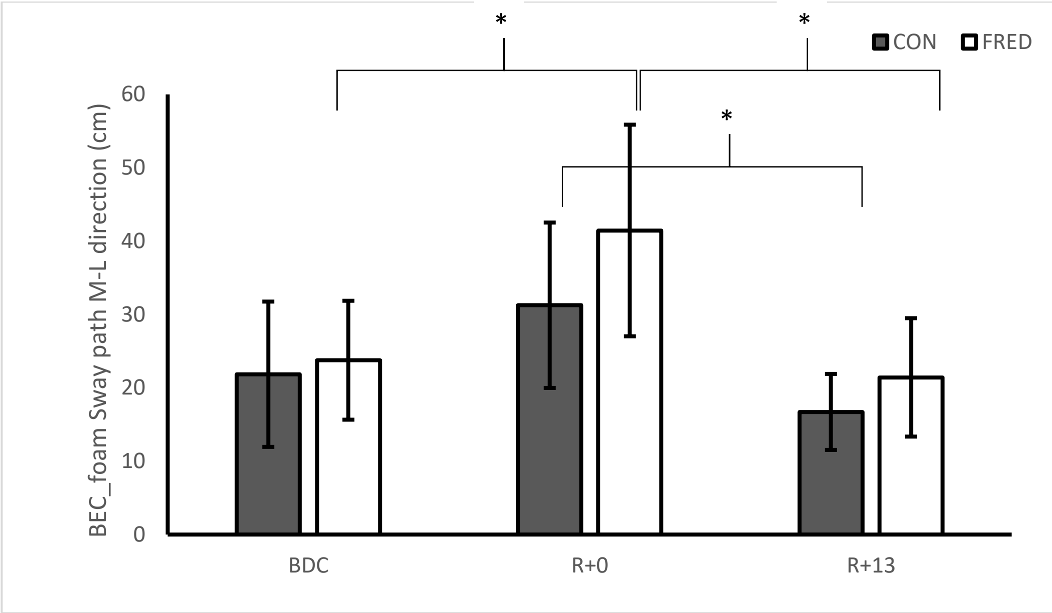


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Figure 9-10 Total sway path length is shown for the bilateral eyes closed foam condition in the M-L direction for FRED (white) and CON (grey) groups at BDC, R+0 and R+13. Data are presented as mean ±SD. * indicates significant differences between time points at p<0.05.

9.2.2 Dynamic Balance Movement Control

A significant main effect of time (Wilk's Lambda = 0.106, F(1,11) = 42.032, p = 0.001) and interaction between group and time (Wilk's Lambda = 0.313, F(2,10) = 10.961, p = 0.003) were observed for dynamic balance movement control, although no main effect of group was found (Wilks Lambda = 0.296, F(1,11) = 26.199, p = 0.704).

A pairwise comparison showed no significant difference in FRED variability between BDC and R+0 (FRED p = 1.000, CON p = 1.000), with trivial effect sizes in both groups (FRED d = 0.04, CON d = 0.02). There was then a significant improvement between R+0 and R+13 for both groups (FRED p = 0.009, CON p = 0.001), with a large effect size in the FRED group (d = -3.09) and a medium effect size in the CON group (d = 0.78) . The R+13 movement variability was significantly different from BDC in both groups (FRED p = 0.001, CON p = 0.001) , with large effect size in the

FRED group (d = -3.28) and a medium effect size in the CON group (d = 0.76), as shown in Figure 9.6 and Table 9.4. Between R+0 and R+13, the CON group movement variability frequency reduced from 0.10±0.31Hz to 0.07±0.28Hz and the FRED group reduced from 0.11±0.022Hz to 0.041±0.01Hz. Previous research has suggested that a change in variability of 0.01Hz was noticeable by some participants.

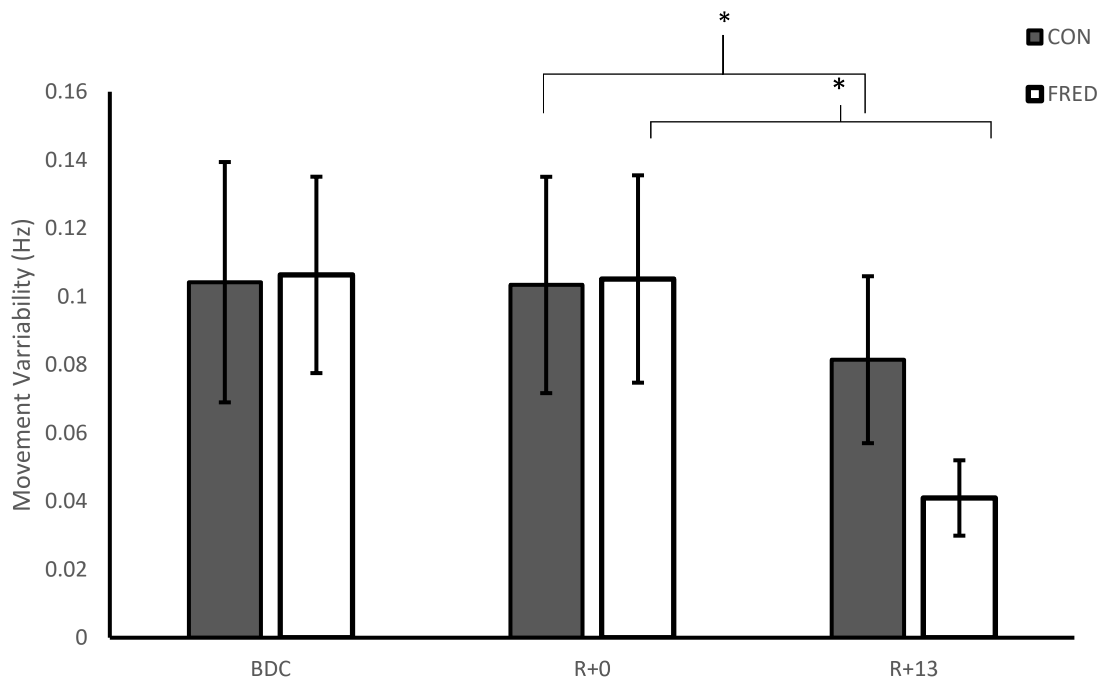

Figure 9-11 FRED movement variability at all time points for both FRED and CON group. HDT did not affect movement variability, but reconditioning did.

9.3 Discussion

The main findings of this chapter were that head-down tilt bed rest (HDT) had a detrimental effect on total sway path length during static balance tasks and that participants in both groups returned to baseline by R+13, which agrees with previous research (Viguier et al., 2009). Thirteen days of FRED exercise plus standard rehabilitation did not benefit standard rehabilitation alone for static balance. In the dynamic movement control task, thirteen days of FRED exercise plus standard rehabilitation improved the dynamic movement control of the FRED group more than the CON group and, interestingly, individuals who did not receive any artificial gravity (AG) countermeasure during HDT benefited from FRED exercise the most. Unexpectedly, HDT did not influence FRED movement control during the dynamic balance task, which disagrees with previous research into functional tasks following bed rest and spaceflight (Miller et al., 2018; Mulavara et al., 2018).

9.3.1 Static balance

Improving postural control is essential because Astronauts experience acute postural challenges upon their return to Earth (Mulavara et al., 2018), which may impede their ability to carry out their activities of daily living. Additionally, on a planetary exploration mission, astronauts will be required to move around the environment in another gravity setting safely (Stuster et al., 2018).

The principal static balance finding in the current study was that total sway path length increased following 60-days of head-down tilt in all balance conditions. It subsequently returned to BDC levels in both groups by R+13, suggesting that FRED did not have an additional benefit compared to standard reconditioning on total sway path length. Between R+0 and R+13, both groups showed significant improvements in total sway path length in the A-P and M-L directions, with medium to very large effect sizes in both groups. The similarities in effect size, the magnitude of change in sway path length and the non-significant differences in total sway path length between BDC and R+13 in the FRED and CON group, suggest that the FRED intervention had only a minimal additional effect on the standard reconditioning program on static balance. However, the individual variability within the groups was large, and lower limb injuries in one-quarter of the group may have masked changes in balance ability. The groups may have behaved similarly because the standard reconditioning program included providing balance training (Lee 2019, private communication).

Previous research has shown that bed rest can induce balance and functional changes and, therefore, can be used to simulate changes following spaceflight (Miller et al., 2018; Mulavara et al., 2018). The balance detriment seen following both spaceflight and HDT originates from neuroplastic changes within the vestibular system (Hupfeld et al., 2020), with an additional component coming from sensorimotor changes (Mulavara et al., 2018). Muavara et al. (2018) found that, after 60-days of HDT, the A-P peak centre of pressure (CoP) excursion increased by 99%, while the A-P velocity increased by 136%. Viguier et al. (2009) found that 60-day HDT affected participants' balance more with their eyes closed, suggesting that vestibular deconditioning, as well as musculoskeletal deconditioning, lead to a deterioration in balance performance. Damiano et al. (2016) found elliptical training was beneficial in improving balance in individuals with Traumatic Brain Injury. However, no such effect was seen in this study with deconditioned but otherwise healthy individuals. This suggests that the standard reconditioning program undertaken by both groups was sufficient to address the deficits in the sensorimotor system resulting from 60-days of HDT, possibly creating a ceiling effect. It may also be that total sway path length, which is a gross measure of balance performance, was not sensitive enough to detect differences between groups.

In the current study, the data interpretation was complicated by several lower limb and back injuries (Table 7.3). Looking at relative differences in the injury-free participants (n = 9/group), three CON group participants in the most challenging BEC_foam A-P condition were worse on the R+13 data collection day than those in the FRED group (Figure 9.12). In the injury-free BEC_foam condition, the FRED group tended to be better with an average sway path length reduction of 30%±22% compared to 14%±27% for the CON group. This pattern was also seen in the BEO_foam A-P condition, with the FRED group showing a 33% ± 22% improvement and CON group showing only an 18% ±27% improvement, suggesting that any difference between FRED and CON groups when including the injured plus non-injured participants may be masked by lower limb and back injuries. Overall, FRED did not appear to be suitable as a primary balance intervention. However, having more time to practice maintaining balance on an uneven surface when FRED is used as an early intervention for pain symptoms (see Chapter 7) and to encourage LM muscle hypertrophy (see Chapter 8) may be beneficial in clinical or astronaut populations as a secondary or adjunct outcome.

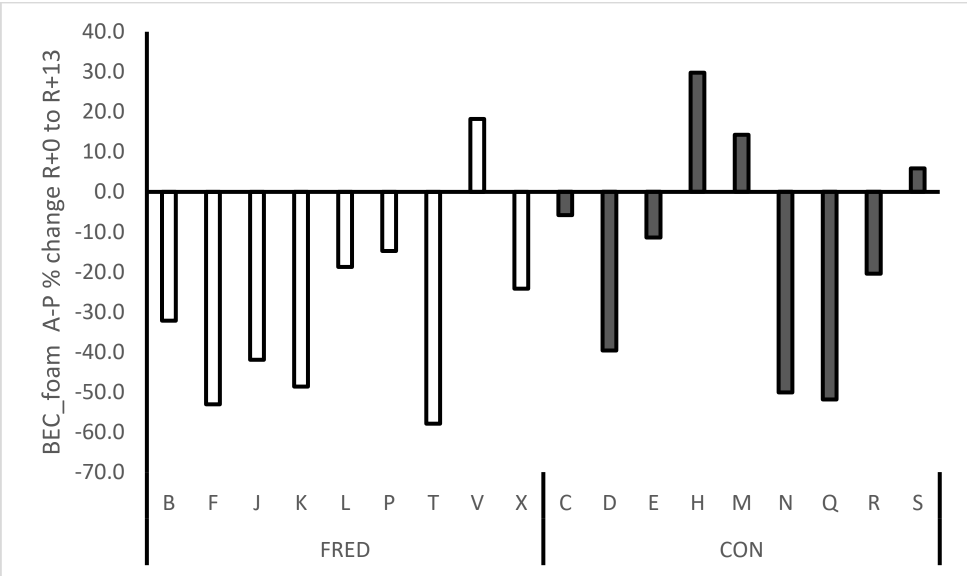

Figure 9-12 Individual relative change in balance between R+0 and R+13in the BEC_foam balance task; a negative number shows an improvement.

9.3.1.1 Limitations of the static balance task

The lack of group effect seen in the static balance task is surprising because it was expected that FRED training would provide additional lower-limb coordination, weight transfer and postural control training, which would be beneficial for a deconditioned population. One possible explanation for the lack of changes seen may be the measure used. The total sway path length is a derived measure that considers the sway velocity and sway duration in only two directions, anteroposterior and mediolateral. However, a more advanced measure such as sway path entropy

(Strang et al., 2011) which considers changes in all directions, may be more suitable for assessing changes in this population considering the complex effects of bed rest intervention, which include musculoskeletal, vestibular, and cardiovascular deconditioning (Scott et al., 2021). Additionally, the number of lower-limb injuries during reconditioning makes interpretation of the data challenging, as the data were collected in standing and were, therefore, influenced by lower limb dynamics. Future studies could reduce this influence by completing the balance tasks in sitting, isolating the dynamic spinal changes from those of the lower limbs, although no evidence was found of sitting balance tests previously being used after bed rest.

9.3.2 Dynamic balance

At R+0, the CON group had a 1.1±14.9% change in movement variability after HDT, while the FRED group had a 0.9±15.8% change, showing that both groups had a minimal change pre-post bed rest, which was unexpected. This result may be due to the nature of the FRED exercise, which encourages the participants to move as slowly as possible, which may have been encouraged by elements of the post-HDT deconditioning such as increased muscle fatiguability in the lower limbs (Gallagher et al., 2005) and pain symptoms during the early re-ambulation period (discussed in Chapter 7). By R+13, the FRED group showed a 59.3±8.6% improvement in variability, while the CON group experienced a 21.4±10.6% improvement. This shows that FRED and CON groups both experienced a learning effect or that dynamic movement control was increased in both groups purely due to the standard reconditioning protocol. The presence of a learning effect is supported by data from the LBP study (discussed in chapter 6.1.1), which shows that between BDC and week 1.1 (three exposures /14 minutes to FRED exercise), participants improved by an average of 0.032 ±0.060 Hz, while the AGBRESA CON participants improved by a 0.022 ± 0.058Hz between R+0 and R+13, three exposures/ 12 minutes on FRED. This suggests that the AGBRESA CON group's changes may have been due to the learning effect alone and not an improvement in neuromuscular control due to standard reconditioning. Future FRED research needs to consider whether training to a plateau before measuring the intervention's effect is required to fully understand the physiological effects of FRED exercise.

Further splitting the participants into their artificial gravity groups, either control (CTRL), continuous (cAG) or intermittent (iAG), revealed that the cAG and iAG groups responded similarly in terms of movement variability (cAG=57.7±7% and iAG=56.6±1.5%). In contrast, the CTRL group responded more with a 63.7±17.2% improvement (Figure 9.13). This suggests that daily exposure to AG during HDT leads to only a small effect of FRED exercise on movement variability; however, for participants who did not receive the AG countermeasure, FRED exercise was even more beneficial.

Using a rapid arm movement task, which was part of the current study but beyond the scope of this thesis, De Martino et al. (2021) showed that intermittent artificial gravity was partially successful at mitigating neuromuscular deconditioning resulting from HDT and helped to maintain anticipatory postural adjustments during the balance tasks in the A-P direction, possibly due to repeated stimulation of the sensorimotor system. Therefore, iAG participants may have shown the least improvement in FRED movement variability because they had less capacity to improve and vice versa for the CTRL/FRED group. The obvious improvement in movement variability in the FRED group, regardless of AG countermeasure, compared to the combined CON group shows that FRED exercise can improve movement variability within two weeks. Therefore, FRED could be used in the current post-flight reconditioning program of NASA or ESA (discussed in Chapter 2) without the need for additional reconditioning program time.

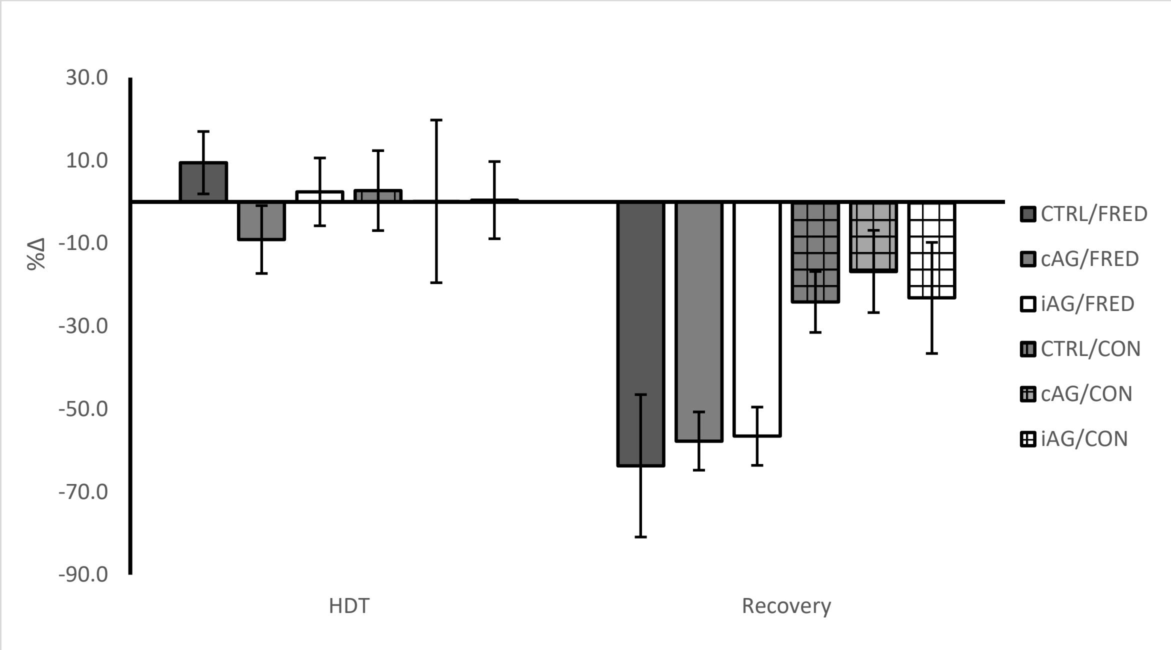

Figure 9-13 Percentage change in movement variability pre-post HDT (HDT) and between R+0 and R+13 (Recovery)

FRED variability seems to be innate and not controlled by the participant in the same way that movement frequency is, with participants frequently expressing annoyance at their performance or perceived flaws in their performance, despite all attempts to keep the user feedback trace they see as smooth as possible. FRED variability appears to be sensitive to change depending on what other training and experiments the participant received before FRED sessions; being well-rested leads to smaller variability and completing physically demanding experiments or reconditioning leads to larger variability (Figure 9.14). The slight movement variability on days R+4 and R+8 occurred on days with microdialysis, which involved four hours supine (R+4) and a rest day (R+8), respectively, while the large variability seen on R+5 and R+12 occurred on days with strenuous testing on MARES, which required repeated 100% MVCs. A general timetable of other training and experiments are given in Table 9.6 for comparison. This leads to the intriguing possibility that FRED could be used as a functional test to monitor fatigue in situations where physical performance is essential, such as military aircrew (Martin et al., 2020).

Table 9-3 Training and testing schedule, which is common to all participants

Day	training schedule	Other testing
R+0	testing day	physical performance, jump, VO2 max, treadmill
R+1	1/2 physio	
R+2	1/2 physio	muscle strength testing
R+3	1/2 physio	
R+4	1/2 physio and reconditioning	Microdialysis (4hrs supine)
R+5	1/2 physio and reconditioning	MARES
R+6	reconditioning	
R+7	reconditioning	
R+8	rest day	
R+9	reconditioning	
R+10	reconditioning	
R+11	reconditioning	
R+12	testing day/ sleep test	MARES

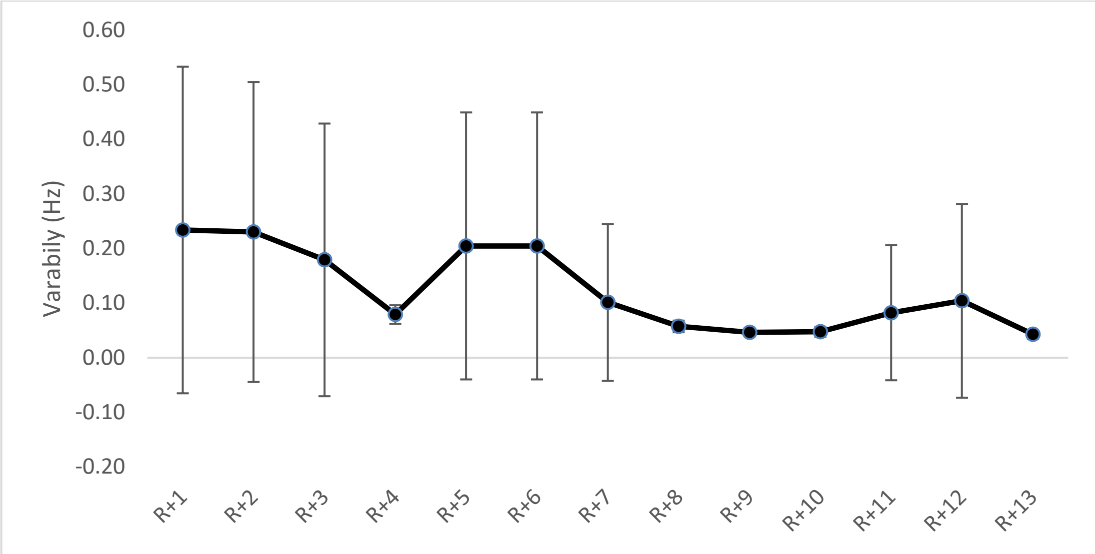

Figure 9-14 FRED group mean ±SD movement variability on each of the recovery days. Days R+4 and R+8 had low levels of physical exertion, and Days 5 and 12 had high levels of physical exertion.

9.3.3 Limitations of the dynamic movement variability task

There were several limitations that may affect the results of the dynamic movement variability task. In Campaign 1, coaching was only given in English, although written instructions were available in German. In Campaign 2, FRED coaching was given in spoken English and German due to a German researcher being available for that campaign. The coaching language may have affected FRED variability due to communication clarity and improved participant understanding, with participants reporting that most felt more confident in the lab when German was used. However, it should be noted that while all participants spoke German fluently, at least four participants spoke it as a second or third language in addition to English, so further research is needed to investigate if coaching in a non-native or home language affects the acquisition of physical skills.

Another element that may affect the outcome of the study is intra-participant competition. While the research team did not encourage competition between participants, some were motivated by the DLR team (bedrest campaign hosts) during the HDT phase by competing against one another, and this continued in the reconditioning phase. Participant B competed with themselves for longer training times each day, continually striving to “beat” their previous time on FRED. In comparison, participants X and U tried to out-perform each other by having the least variable FRED trace. Participant G (female) tried to out-perform all the male participants. This competition may have improved variability because the FRED participants discussed techniques to minimise their trace movement, for example, following the bottom boundary line, despite not being advised to do so. It may also have encouraged participants to minimise their rest breaks to maximise their on-FRED time.

Two FRED machines were used for the experiment; FRED for training and FREDa for data collection. However, an unexpected physiological tremor in some participants led to FRED resonating and the data signal being lost or attenuated due to the rotary encoder moving away from the flywheel. All participants affected were male with a mean height of 182±4cm. A discussion with the DLR team suggested the tremor frequency could be related to hamstring length, as it had been seen in previous bed-rest studies, although these data are unpublished (Mulder, private communication, 2019). The issue was corrected by using additional masses to the FRED flywheel housing (25Kg) and handles (5Kg) as a detuning measure, moving the natural frequency of structure away from problematic frequencies (Figure 9.15). Wiring inside the control box was also replaced to minimise signal loss due to wires being shaken loose with the vibration issue. This meant that some training sessions were completed on FREDa and, while no training time was lost, differences between the machines, such as bearing or footplate resistance, may have affected the movement variability for those sessions.

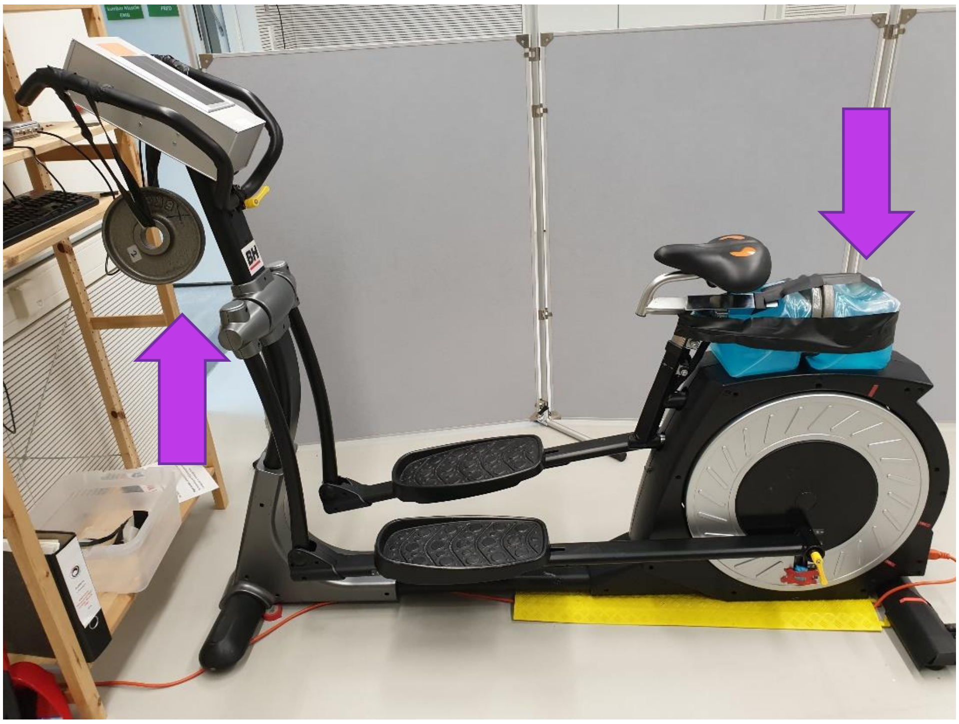

Figure 9-15 FRED detuning measures. Weights were added to the rear flywheel housing to lower the resonate frequency outside of the physiological range, while a free-hanging weight was added to the handles at the front to act as a pendulum counterweight, dampening the remailing oscillations at the front of the FRED. Additional weight is shown with purple arrows.

9.4 Conclusion

This chapter has discussed the effects of 13 days of FRED exercise the following head-down tilt bedrest on static balance and dynamic movement control. Static balance was assessed using the total sway path length for 60 seconds in various bilateral and single-leg balance conditions, which included firm and compliant surfaces with both eyes open and eyes closed. Dynamic movement control was assessed using the average FRED variability over 60 seconds. The main findings of this chapter were that FRED exercise did not significantly affect static balance in either the anteroposterior or mediolateral direction in any balance condition compared to standard reconditioning alone.

FRED exercise significantly improved movement variability and, presumably, neuromuscular control compared to the CON group. However, further research is needed to determine whether the additional improvement in movement variability measured during FRED exercise in the FRED group was due to physiological training effects or simply additional familiarisation resulting from daily reconditioning on FRED. There is some intriguing evidence that suggests that FRED exercise has a potential role in assessing and monitoring physical fatigue from other tasks, although research is required to explore this further. Additionally, when considering the artificial gravity countermeasure, participants receiving FRED reconditioning after HDT with no AG countermeasure (control AG group) matched the movement variability of those participants who had received either continuous or intermittent AG countermeasure. This suggests that FRED may have a beneficial post-flight reconditioning role in situations where in-flight countermeasures are unavailable or limited, as it was able to improve movement variability within two weeks independent of countermeasure exposure during HDT.

10 Chapter 10 Thesis Conclusion

This thesis aimed to determine whether the Function Re-adaptive Exercise Device (FRED) effectively improves lumbopelvic structure and function in populations modelling the lumbopelvic deconditioning effects seen in astronauts post-flight, namely chronic non-specific low back pain and 60-day Head-down tilt bed rest. The thesis focused on the effectiveness of the FRED as a reconditioning tool for Lumbar Multifidus and Transversus Abdominis muscle atrophy, back pain, static balance and dynamic movement control and function. Two studies were undertaken, each modelling a different part of space induced lumbopelvic deconditioning; the first study used the concept of reciprocal knowledge transfer in a chronic non-specific low back pain population (Chapters 4 to 6) and the second study used 60 days of head-down tilt bed rest as a spaceflight simulation (Chapters 7 to 10).

10.1 Original Contribution to Knowledge

This thesis has made an original contribution to knowledge in several different areas, which are discussed below. It is the first time that the FRED has been used in a clinical low back pain population and the first time that FRED has been used as an early reconditioning exercise intervention following head-down-tilt bed rest.

10.2 Patient-Reported Outcome Measures

10.2.1 Functional ability

Six weeks of FRED exercise, three times a week for up to 30 minutes, improved patient-reported function in people with chronic, non-specific low back pain for activities of daily living, as measured on the patient-specific functional scale. Improvement was seen in a wide range of activities, including standing, sitting, bending, lifting and twisting, and physically demanding sports activities. All participants in the LBP study reported improvements in at least one activity of daily living following the FRED intervention. These improvements exceeded the minimum clinically important difference threshold, with improvements being maintained at six- and 15-week follow-up.

10.2.2 Pain

Despite no changes in pain intensity were recorded in the LBP study, anecdotal evidence from the participants suggested that FRED exercise may reduce the duration of symptoms and potentially the intensity of pain symptoms in chronic non-specific low back pain, with a clinically meaningful but not statically significant reduction in the numeric rating scale for pain score seen immediately post-intervention. In the AGBRESA study, therefore, questionnaires enabled participants to indicate the duration of pain symptoms and the location and intensity of pain. It was confirmed that people undertaking FRED exercise during the early reconditioning period following bedrest experienced lower pain intensity, lower numbers of reports of back pain, and reduced symptom duration compared to controls. Interestingly, the pain area was increased in the FRED group, which may be due to the increased standing and exercise time undertaking FRED exercise. The reduction in pain seen as a result of using FRED may be linked to postural improvements, such as spinal alignment and pelvic tilt, or due to exercise-induced analgesia.

An important finding from the AGBRESA study is that a reduction in Lumbar Multifidus cross-sectional area as measured on MRI at the L5/S1 level was not linked with the experience of acute pain during bed rest in this population. This supports the findings of Harrison et al. (2018), who suggested that the experience of space adaptation back pain was not temporally linked to deconditioning post-flight. Post-flight deconditioning is dangerous in the astronaut population because it is silent; the experience of pain does not act as a warning to inform individuals that they are in a deconditioned state, and they may, therefore, undertake activities which they are not physiologically capable of completing safely. The silent nature of deconditioning may be one reason why there is an increase in spinal injuries seen in the first year post-flight (Johnston et al., 2010).

The current data support the use of FRED exercise in both the chronic non-specific low back pain patient population and simulated post-flight astronaut population to decrease back pain symptoms. However, the role that FRED may play in central sensitisation and, therefore, increased pain area needs to be explored further.

10.2.3 Lumbar Multifidus and Transversus Abdominus muscle size changes following FRED intervention.

10.2.3.1 Lumbar Multifidus

Both studies found that FRED was able to increase LM CSA. In the AGBRESA study, there was a significant group effect, with the FRED group increasing more on average. However, not all participants responded positively to FRED exercise, and individual variation was high. The LBP study observed an increase in the Lumbar Multifidus cross-sectional area on the left-hand side of the body following FRED intervention, while this was observable but non-significant in the AGBRESA study. FRED exercise appears to be a suitable reconditioning tool in both chronic non-specific low back pain and post-flight. Importantly for spaceflight reconditioning, two weeks of up to 30 minutes per day positively affect the Lumbar Multifidus size at the L5/S1 level. Current data support the idea that FRED exercise is a useful reconditioning tool for the Lumbar Multifidus cross-sectional area.

10.2.4 Transversus Abdominis

Ultrasound imaging of the transversus abdominis failed to find significant changes in muscle thickness at rest, 100%, or 30% maximum voluntary contraction in either the low back pain study or the AGBRESA study. Interestingly, in contrast, previous research suggested that head-down tilt bed rest did not have a detrimental effect on TrA thickness (Belavý et al., 2010). This may have been mitigated using the anti-G straining manoeuvre during the artificial gravity countermeasure in the current study. Current data do not support the idea that FRED is a useful reconditioning tool for the transversus abdominis muscle, although it is not detrimental to this muscle.

10.2.5 Static balance

Neither the low back pain study nor the AGBRESA study found statistically significant effects of FRED exercise on total sway path length in either the anterior-posterior or mediolateral direction. This finding may be due to the limited transferability of the dynamic FRED movement cycle into static balance, or it may be due to the total sway path length being insufficiently sensitive to detect balance changing following FRED intervention. A more sophisticated measure such as sway path analysis may elucidate balance changes following FRED exercise. At present, the available data do not support the use of FRED exercise as an intervention to improve static bipedal balance in either chronic low back pain or a deconditioned simulated astronaut population. The effect of FRED on single leg balance was also considered. However, the majority of participants were unable to complete the required minimum of 60 seconds of single-leg standing needed to complete the data collection, so it is not possible to determine if FRED exercise affects single-leg balance.

10.2.5.1 Dynamic balance and movement variability the standard measure of neuromuscular control

FRED movement variability, calculated as the standard deviation from the target frequency over 60 seconds, improved following the FRED intervention in both studies, with the FRED group improving more than the CON group in the AGBRESA study. Movement variability was assumed to be a surrogate measure of neuromuscular control, as improved variability requires more co-ordination and movement control than a larger variability. Improved movement variability and, by extension, neuromuscular control suggests that FRED could be used as a reconditioning tool in both chronic non-specific low back pain and post-flight astronaut populations. Interestingly, in the AGBRESA study, the participants in the artificial gravity control group (i.e. no AG) who undertook FRED training had similar movement variability to those individuals who received the artificial gravity intervention by R+13, and they showed the greatest improvement in movement variability of any group during the reconditioning period. This result suggests that on missions in which it is challenging to undertake in-flight countermeasures, FRED could be a helpful tool in reconditioning neuromuscular control in the post-flight period. Additional results suggest that FRED variability is nonvolitional in nature; it cannot be controlled consciously by the individual so that FRED frequency can. There is also a potential floor effect in movement variability at around 0.02 Hz, after which improvement does not appear to be possible.

10.2.6 Limitations

Numerous limitations to different aspects of the experiments in this thesis have been discussed in individual chapters. An overarching limitation that affected both studies was low participant numbers, with a sample size of 14 in the low back pain study and 24 in the bedrest study. The issue of low participant numbers is commonplace in the space physiology field due to the availability of specialist facilities such as envihab used during the AGBRESA study or, indeed, access to the International Space Station. Future FRED research would benefit from larger sample sizes, potentially staggered over multiple bedrest campaigns to limit the effect of staff and lab resource availability. A larger sample size would allow for clearer predictive statistics to clarify the effects of FRED exercise while minimising the effect of individual variability and injuries, both of which have affected the results of this thesis.

Future direction of FRED research.The experiments presented in this thesis have highlighted several areas of interest for future FRED research. One relatively new field of study is pain perception after low-intensity exercise (Hviid et al., 2019). Self-reported pain findings from the AGBRESA study suggested that FRED may have a positive role in pain management. Further, more detailed research is needed to explore exercise-induced analgesia in low-intensity exercise such as FRED.

In the AGBRESA study, the control group who did not receive FRED exercise training showed improved movement variability by the end of the study. This finding suggests that a learning effect is present, even with low levels of exposure. Future research, therefore, needs to explore whether it is more useful to have participants trained before data collection to minimise the learning effect as this would allow for analysis from a steady state of movement variability.

In both studies, FRED exercise influenced the cross-sectional area of the left Lumbar Multifidus more than the right. Further research is, therefore, needed to determine what mechanical changes are needed to FRED to encourage an equal use of the Lumbar Multifidus during training. Adjustments such as differential resistance on each side to optimise FRED for individual use may be beneficial. Consideration may also need to be taken in the future design of FRED to ensure that the resonance frequency of the machine is not within the physiological range during muscle fatigue to prevent the tremor-induced vibrations that led to signal loss in the AGBRESA study.

Finally, there were also intriguing data from the AGBRESA study, which suggested that FRED may have a role in detecting and monitoring fatigue in situations where physical performance is required. This is a new and unexpected potential direction for FRED use and research. Potential future investigations could combine cognitive and physical fatigue performance metrics to determine which types of fatigue affect FRED performance and whether FRED movement variability is sensitive enough to be used as part of fatigue testing battery. FRED may have a benefit over traditional fatigue measuring methods because it appears that FRED movement variability non-volitional.

10.3 Practical applications for astronaut and wider terrestrial reconditioning

The research undertaken in this thesis suggests that there are future practical applications for FRED exercise in both astronaut and terrestrial populations. Daily FRED exercise for two weeks had a positive impact on pain intensity and symptom duration. This effect could be helpful in clinical populations where rehabilitation time is available in small but intense blocks in either the in-patient or out-patient settings. FRED exercise improved the self-reported function of all the participants in the Low Back Pain Study, generally by at least twice the Minimal Clinically Important Difference of the Patient-Specific Functional Scale. This suggests that FRED exercise would fit into the Public Health England All Our Health Framework (PHE, 2019), which aims to promote good musculoskeletal health practices, including preventative and intervention measures that support healthy ageing and maintain physical activity and function UK population.

The ability of FRED to reverse Lumbar Multifidus deconditioning suggests that it has a role to play in post-flight reconditioning. All the participants in both studies learned how to use FRED safely with minimal coaching; therefore, FRED appears to be suitable for unsupervised use after the initial training session. Using FRED unsupervised would allow FRED to be used in rehabilitation, astronaut, or commercial gyms as a self-management tool. One way to make FRED more commercially viable would be to combine a no-resistance FRED setting within a variable resistance elliptical-trainer that was able to provide both FRED control training and resistive cardiovascular exercise, rather than a stand-alone FRED only device.

The newly discovered sensitivity of FRED movement variability to fatigue suggests a range of potential future uses. One potential client group for fatigue monitoring is military aircraft, as both high levels of physical fitness and fatigue management are necessary for the safe completion of military sorties (Martin et al., 2020).

Overall, FRED shows promise as a rehabilitation tool for both post-flight astronauts and low back pain patients. These proof-of-concept experiments have shown that FRED can provide positive outcomes when used as a reconditioning tool for back pain, Lumbar Multifidus size and dynamic movement variability. Intriguing new data suggest FRED may have a role to play in monitoring physical fatigue, and this is a new and exciting direction for future FRED research: to boldly go where no elliptical trainer has gone before.

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Appendix A: Search strategy for literature review

A systematic search of the literature was undertaken in March 2018 and re-run in April 2020 and again in June 2021. CINAHL with Full Text, AMED, eBook Collection (EBSCOhost), Ergonomics Abstracts, Library, Information Science & Technology Abstracts, SPORTDiscus and Web of Science databases were included in the search. Keywords included: back or spin(e/al), space flight, spaceflight, microgravity, astronaut(s), cosmonaut(s), and exercise or countermeasure(s) or rehabilitation. Bed Rest and head-down Bed Rest were used as separate search terms initially, but no new papers were identified. Inclusion criteria were: human spaceflight or spaceflight simulation, exercise or countermeasure, musculoskeletal, peer-reviewed article and included countermeasures used after 2009, in English. BR studies were not time-limited, as ARED availability does not impact these studies findings. The exclusion process is shown in more detail below (Moher et al., 2009), which resulted in 36 articles being included in this review. The June 20121 search identified one addition paper, bringing the total included to 37.

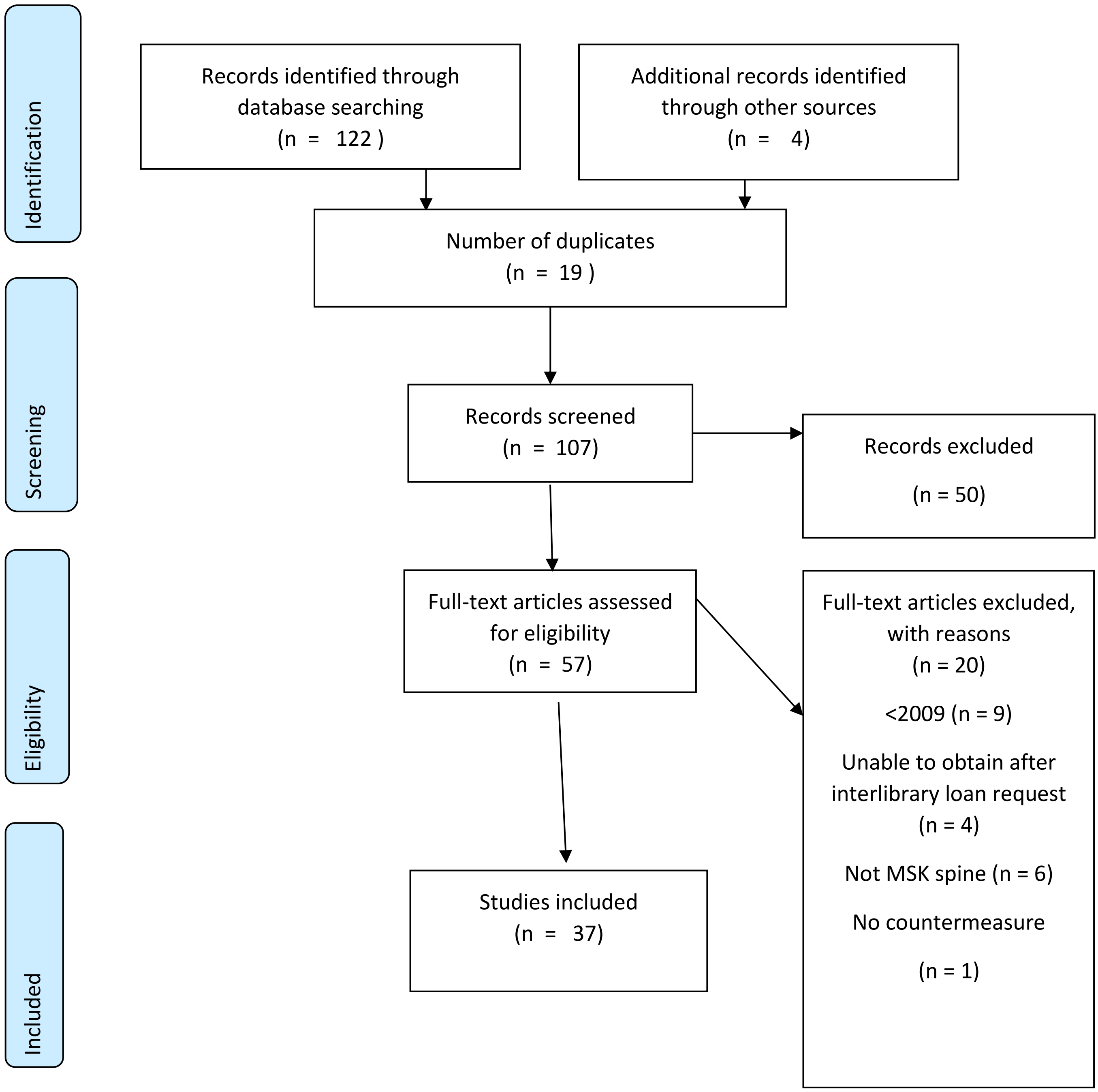


Figure A PRISMA diagram of search process

Appendix B: Activity Log Questionnaire

Question	Further information given	Type of answer required	Answer choices available
How physically active were you yesterday?	If you have chosen 'not active', please skip the next question.	Text required	1.Not Physically active 2. Very Light (e.g. standing in lectures, etc.) 3. Light (e.g. hoovering, walking etc.) 4. Moderate (e.g. jogging/running etc.) 5. Vigorous (e.g. badminton/squash etc.)
How long were you physically active?	Please write the number of the activity level (1. not active 2. v. light, 3. light, 4. moderate, 5. vigorous) and the total number of minutes at that activity level, e.g. 2- 15 min, 1- 1hr.	text required	
Was yesterday a typical or unusual day for you?	An unusual might include feeling unwell or being on holiday. If you have selected 'typical day', please skip the next question	choice required	Typical day (default) Unusual day
Why was your day unusual?	e.g. did you feel unwell, did you visit a healthcare professional for something other than your back, were you on holiday, or did you do another activity you only do occasionally?	text optional	
Did you see a healthcare professional about your back yesterday?		choice required	No (default) Yes- Physio Yes- Chiropractor Yes- Osteopath Yes- Doctor Yes- Massage Therapist Yes-Other
Did you take painkillers yesterday?		choice required	No (default) Yes- it was for my back Yes- it was for something other than my back

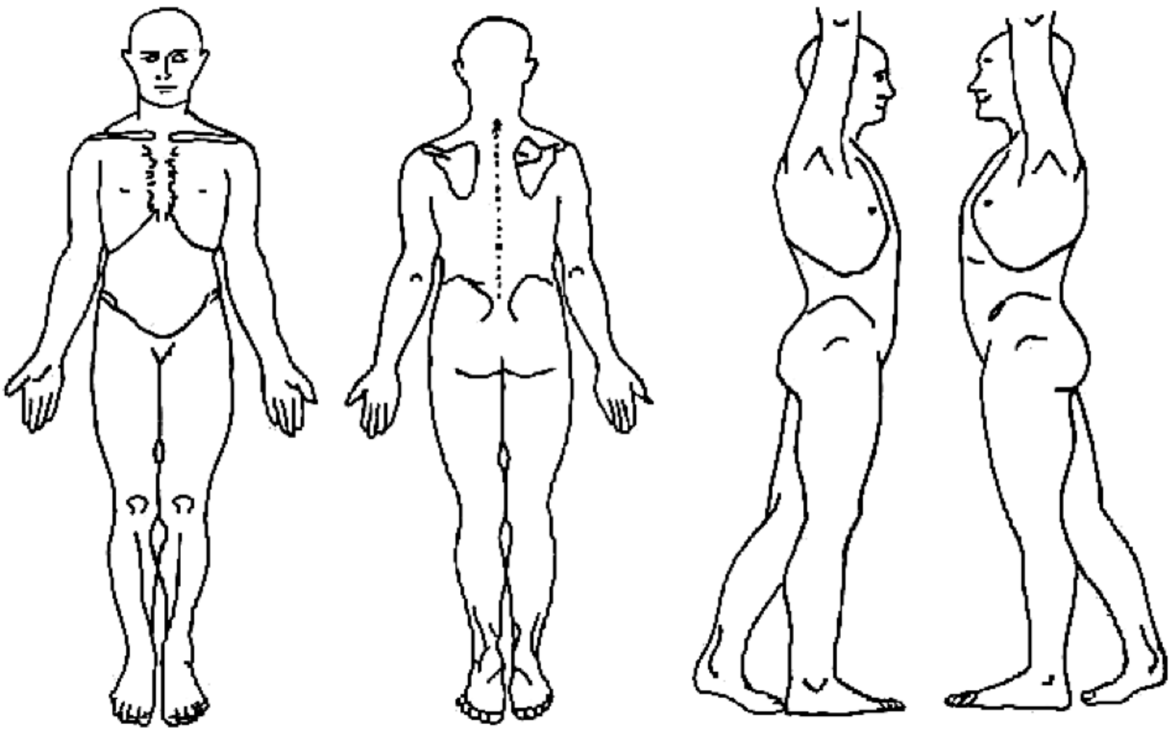
If 'Yes, what type of pain killer did you take?	choice optional	Personal medicine choice, e.g. diclofenac or heat pack Paracetamol Ibruprofen/Neurofen Other
And how much pain killer did you take?	choice optional	Less than my normal dose My normal dose More than my normal dose

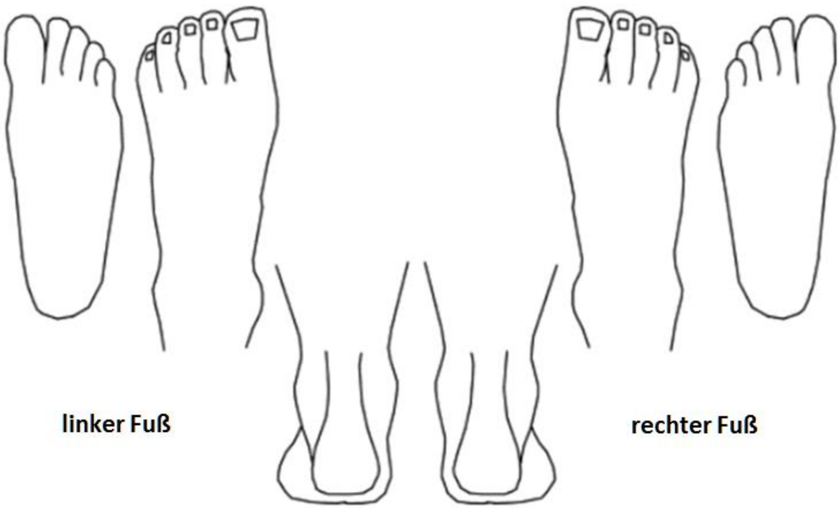
Appendix C: German language Pain questionnaire

Schmerzfragebogen

1. Hatten Sie in den **letzten 24 Stunden** Schmerzen im Muskel, Knochen oder Gelenk, einschließlich Fuß/Sprunggelenk? JA NEIN

2. Falls 'Ja', bitte, markieren Sie auf den folgenden Zeichnungen, in welcher Region Sie diesen spüren. **Jede Region bitte nummerieren.**





3. Für jede dieser Regionen, bitte beantworten Sie auf den folgenden Seiten die Fragen zu Ihren Schmerzen. Ihre Kommentare helfen uns, Ihre Schmerzen noch besser zu verstehen

Region 1:

keine Schmerzen	schlimmste Schmerzen

Schmerzqualität: (z.B. dumpf, scharf, brennend, einschießend, anderes)

Schmerzdauer letzte 24h (in Stunden):

0 – 0,5	0,5 - 1	1-2	2-3	3-4	4-5	5-6	6-8	8-10	10-12	> 12

❒ am Stück ❒ in mehreren Episoden Episodendauer: ______________

Wann ist dieser Schmerz am stärksten?

❒ morgens ❒ mittags ❒ abends ❒ sonstiges_____________________________

Was verschlimmert diesen Schmerz?

____

Was erleichtert diesen Schmerz?

____

Kommentar:

Appendix D: Previous Bed Rest Studies and the papers published from each study.

Table D: All Identified bed rest study papers from all space agencies published in English, from Laws et al unpublished data.

Author(s)	Study Name	Intervention	N (total)	Length (days)	tilt angle	Outcome measure(s)	space agency
Hughson, Maillet, et al. (1994)	1990/91 MEDES study	RE + LBNP	12 male	28	hdt with head-up exercise	Cardiovascular	CNES,
Hughson, Yamamoto, et al. (1994)	1990/91 MEDES study						
Armbrecht et al. (2010) DLR"	BBR	RVE	20 male	56	horizontal	Skeletal	"ESA
Belavý et al. (2008)	BBR					Muscle & Skeletal	
Belavý et al. (2009)	BBR					Muscle	
Belavý et al. (2012)	BBR					Muscle	
Blottner et al. (2006)	BBR					Muscle	
Buehring et al. (2011)	BBR					Muscle	
Dilani Mendis et al. (2009)	BBR					Muscle	
Mulder et al. (2006)	BBR					Muscle	
Mulder et al. (2008)	BBR					Muscle	
Rittweger et al. (2006)	BBR						
Rittweger et al. (2010)	BBR					Muscle & Skeletal	
Sun et al. (2015)	BBR					Skeletal	
van Duijnhoven et al. (2008)	BBR					Cardiovascular	

Bleeker et al. (2005)	subpopulation of BBR	RE or RVE	16 male 24 male	60	hdt	Cardiovascular	"ESA
Belavý et al. (2010)	BBR2					Muscle & Skeletal	
DLR"							
Belavý et al. (2016)	BBR2					Skeletal	
Belavy, Beller, Ritter, and Felsenberg (2011)	BBR2					Skeletal	
Belavý, Gast, and Felsenberg (2017)	BBR2					Muscle & Skeletal	
Miokovic et al. (2014)	BBR2					Muscle	
Mulder et al. (2009)	BBR2					Muscle	
Salanova et al. (2013)	BBR2					Muscle	
Salanova et al. (2014)	BBR2					Muscle	
van Duijnhoven, Green, et al. (2010)	BBR2					Cardiovascular	Astronaut Centre of China
van Duijnhoven, Thijssen, et al. (2010)	BBR2	RVE + vibration	14 male	60	hdt	Cardiovascular Cardiovascular	
Coupé et al. (2011)	Earth Star International Bed Rest Experiment Project						
Wang et al. (2012)	Earth Star International Bed Rest Experim	RVE FW	14 male	60 90	hdt hdt	Skeletal	ESA, CNES, NASDA

	ent Project						
Yang et al. (2014)	Earth Star International Bed Rest Experiment Project		18 male 25 male				
Reeves, Maganaris, Ferretti, and Narici (2005)	LTBR 2000-2001					Muscle	
Rittweger and Felsenberg (2009)	LTBR 2000-2001					Muscle & Skeletal	
Rittweger et al. (2005)	LTBR 2000-2001					Muscle & Skeletal	
Rittweger, Felsenberg, Maganaris, and Ferretti (2007)	LTBR 2000-2001					Muscle	
Rittweger, Moller, Bareille, Felsenberg, and Zange (2013)	LTBR 2000-2001					Muscle	
Rudnick et al. (2004)	LTBR 2000-2001	Horizontal sledge jump system	22	60	hdt	Muscle	ESA, DLR
Koschate, Thieschäfer, Drescher, and Hoffmann (2018)	Reactive jumps					Cardiovascular	
Koschate, Thieschäfer, Drescher, and	Reactive jumps		23 male			Cardiovascular	

Hoffmann (2018)							
Kramer, Gollhofer, Armbrecht, Felsenberg, and Gruber (2017)	Reactive jumps					Muscle & Skeletal & Cardiovascular	
Kramer, Kuemmel, et al. (2017)	Reactive jumps					Cardiovascular	
Maggioni et al. (2018)	Reactive jumps		"12 sets of twins			Cardiovascular	
Cao et al. (2005)	twin study	Treadmill LBNP					
14 female							
10 male"	28	hdt	Skeletal	NASA and NIH			
Macias, Cao, Watenpaugh, and Hargens (2007)	twins study	Treadmill LBNP				Skeletal	
Zwart et al. (2007)	twins study	Treadmill LBNP				Skeletal	
Smith et al. (2003)	twin study	Treadmill LBNP	16	30	hdt	Skeletal	NASA, NIH
Bamman et al. (1998)		Horizontal leg press training device	16 male	14	hdt	Muscle	NASA and NIH
Bamman, Hunter, Stevens, Guilliams, and Greenisen (1997)	as Bamman et al 1998	Horizontal leg press training device		14	hdt	Muscle	NASA and NIH

Ploutz-Snyder et al. (2018)	twins study	Zero-gravity Treadmill + Cycle ergometer or FW	34	70	hdt	Muscle & Skeletal & Cardiovascular	NASA
Schneider et al. (2002)	twins study	Treadmill LBNP	7 male	15	hdt	Cardiovascular	NASA
Schneider et al. (2016)	twins study ULLS and HDT,	Treadmill LBNP	30 male and female 17 male 16 female 24 female	30 90 60 60	hdt ULLS and HDT hdt hdt	Muscle & Cardiovascular	NASA NASA, NIH , ESA, NASDA , CNES
Haus, Carrithers, Carroll, Tesch, and Trappe (2007)	only hdt in table subset of WISE 2005 WISE 2005	FW				Muscle	ESA, NASA, CNES, CSA ESA,NASA , CSA, CNES
Arinell, Christensen, Blanc, Larsson, and Fröbert (2011)		FW + Treadmill				Cardiovascular	
Arbeille, Kerbeci, Mattar, Shoemaker, and Hughson (2008)		FW + Treadmill LBNP				Cardiovascular	
Armbrecht et al. (2011)		FW + Treadmill LBNP				Skeletal	
Choppard et al 2009		M-MED				muscle	
Demiot et al. (2007)		Treadmill LBNP				Cardiovascular	
Dorfman et al. (2007)		Treadmill LBNP				Cardiovascular	
Guinet et al. (2009)		Treadmill LBNP				Cardiovascular	
Holt et al. (2016)		FW + Treadmill LBNP				Muscle	
Kuj et al 2012		FW + Treadmill LBNP				Cardiovascular	

Lee et al. (2014)	FW + Treadmill LBNP				Muscle	
Salanova, Schiffl, Püttmann, Schoser, and Blottner (2008)	FW				Muscle	
Smith et al. (2008)	FW + Treadmill LBNP RE				Skeletal	
Trappe et al. (2008)	Gravity-independent inertial ergometer				Muscle	
Trappe, Burd, Louis, Lee, and Trappe (2007)					Muscle	
Akima, Kubo, et al. (2000)	Horizontal leg press training device	9 male	20	hdt	Muscle	" NASDA, and the
Japan Space Forum."						
Akima et al. (2003)		12 male			Muscle	
Shinohara, Yoshitake, Kouzaki, Fukuoka, and Fukunaga (2003)					Muscle	
Alkner et al. (2004)	FW	17 male	90	hdt	Muscle	SNSB, ESA NASDA, CNES
Baeker et al 2012	RVE	8 male	14	hdt	skeletal	DLR
Belin de Chantemèle et al. (2004)	FW	18 male	90	hdt	Cardiovascular	ESA, CNES, NASDA
Cavanagh et al. (2016)	Zero-gravity treadmill	male and female (12 enrolled)	84	hdt	Muscle & Skeletal	NASA and NIH

Chopard et al. (2005)		FW	"21 male				
"	90	hdt	Muscle	ESA, the CNES, NASDA			
Crandall, Shibasaki, Wilson, Cui, and Levine (2003)		Cycle ergometer	20 (17 male 3 female)	14	hdt	Cardiovascular	NASA and NIH
Ferrando, Tipton, Bamman, and Wolfe (1997)		Horizontal leg-press training device	12 male	14	hdt	Muscle	NASA and NIH
Germain, Güell, and Marini (1995)		Ergocycle + Ergometer	12 male	28	hdt with supine exercise	Muscle	MEDES and CNES
Greaves, Arbeille, Guillon, Zuj, and Caiani (2019)		RVE	12 male	21	hdt with supine testing	Cardiovascular	Italian Space Agency, MEDES, CNES, ESA
Hastings et al. (2012)		Rowing ergometer + RiPP Pro Device	27 male and female	5wks	hdt	Cardiovascular	NASA
Kawakami et al. (2001)		RE	9 male	20	hdt	Muscle	NASDA
Kenny et al. (2017) Kenny et al. (2020)		Integrated training device + whole body vibration Integrated training device + whole body vibration and nutrian	9 male "8 male	21	hdt	Muscle & Cardiovascular	ESA, Enterprise Ireland, CNES, DLR
"	28	hdt	Muscle & Cardiovascular	ESA, Enterprise Ireland, CNES, DLR			

Koppelmans et al. (2018)	Compact FW rowing and resistive exercise device	18	70	hdt	Muscle	NASA and NIH
Kouzaki et al. (2007)	Horizontal leg-press training device	12 male	20		Muscle	NASDA
Krainski et al. (2014)	Rowing ergometer + Schwinn RippPro device	27	5wks	hdt	Muscle	NASA
Mulder et al. (2014)	Locomotion replacement training	10 male	5	hdt	Cardiovascular	DLR
Mulder et al. (2015)					Muscle & Skeletal	
Scott et al. (2018)	Zero-gravity Treadmill + Cycle ergometer + Horizontal exercise fixture	26	70	hdt	Cardiovascular	NASA