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EXPLORATION OF DIGITAL BIOMARKERS IN CHRONIC LOW BACK PAIN AND PARKINSON'S DISEASE

Sammeli Liikkanen

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to all those brave warriors who are enduring chronic pain and Parkinson's disease

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ABSTRACT

Chronic pain and Parkinson's disease are illnesses with personal disease progression, symptoms, and the experience of these. The ability to measure and monitor the symptoms by digitally and remotely is still limited. The aim was to study the usability and feasibility of real-world data from wearables, mobile devices, and patients in exploring digital biomarkers in these diseases. The key hypothesis was that this allows us to measure, analyse and detect clinically valid digital signals in movement, heart rate and skin conductance data.

The laboratory grade data in chronic pain were collected in an open feasibility study by using a program and built-in sensors in virtual reality devices. The real-world data were collected with a randomized clinical study by clinical assessments, built-in sensors, and two wearables. The laboratory grade dataset in Parkinson's disease was obtained from Michael J. Fox Foundation. It contained sensor data from three wearables with clinical assessments. The real-world data were collected with a clinical study by clinical assessments, a wearable, and a mobile application. With both diseases the laboratory grade data were first explored, before the real-world data were analyzed.

The classification of chronic pain patients with the laboratory grade movement data was possible with a high accuracy. A novel real-world digital signal that correlates with clinical outcomes was found in chronic low back pain patients. A model that was able to detect different movement states was developed with laboratory grade Parkinson's disease data. A detection of these states followed by the quantification of symptoms was found to be a potential method for the future. The usability of data collection methods in both diseases were found promising.

In the future the analyses of movement data in these diseases could be further researched and validated as a movement based digital biomarkers to be used as a surrogate or additional endpoint. Combining the data science with the optimal usability enables the exploitation of digital biomarkers in clinical trials and treatment.

KEYWORDS: Chronic pain, Parkinson's disease, Real-world data, Digital biomarkers, Digital Therapeutics

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TIIVISTELMÄ

Krooninen kipu ja Parkinsonin tauti ovat oireiden, oirekokemuksen sekä taudin kehittymisen osalta yksilöllisiä sairauksia. Kyky mitata ja seurata oireita etänä on vielä alkeellista. Väitöskirjassa tutkittiin kaupallisten mobiili- ja älylaitteiden hyödyntämistä digitaalisten biomarkkereiden löytämisessä näissä taudeissa. Pääolettamus oli, että kaupallisten älylaitteiden avulla kyetään tunnistamaan kliinisesti hyödyllisiä digitaalisia signaaleja.

Kroonisen kivun laboratorio-tasoinen data kerättiin tätä varten kehitettyä ohjelmistoa sekä kaupallisia antureita käyttäen. Reaaliaikainen kipudata kerättiin erillisen hoito-ohjelmiston tehoa ja turvallisuutta mitanneessa kliinisessä tutkimuksessa sekä kliinisiä arviointeja että anturidataa hyödyntäen. Laboratorio-tasoinena datana Parkinsonin taudissa käytettiin Michael J. Fox Foundationin kolmella eri älylaitteella ja kliinisin arvioinnein kerättyä dataa. Reaaliaikainen data kerättiin käyttäen kliinisia arviointeja, älyranneketta ja mobiilisovellusta. Molempien indikaatioiden kohdalla laboratoriodatalle tehtyä eksploratiivista analyysia hyödynnettiin itse reaaliaikaisen datan analysoinnissa.

Kipupotilaiden tunnistaminen laboratorio-tasoisesta liikedatasta oli mahdollista korkealla tarkkuudella. Reaaliaikaisesta liikedatasta löytyi uusi kliinisten arviointien kanssa korreloiva digitaalinen signaali. Parkinsonin taudin datasta kehitettiin uusi liiketyyppien tunnistamiseen tarkoitettu koneoppimis-malli. Sen hyödyntäminen liikedatan liiketyyppien tunnistamisessa ennen varsinaista oireiden mittausta on lupaava menetelmä. Käytettävyys molempien tautien reaaliaikaisissa mittausmenetelmissä havaittiin toimivaksi. Reaaliaikaiseen, kaupallisin laittein kerättävään liikedataan pohjautuvat digitaaliset biomarkkerit ovat lupaava kohde jatkotutkimukselle. Uusien analyysimenetelmien yhdistäminen optimaaliseen käytettävyyteen mahdollistaa tulevaisuudessa digitaalisten biomarkkereiden hyödyntämisen sekä kroonisten tautien kliinisessä tutkimuksessa että itse hoidossa.

AVAINSANAT: Krooninen kipu, Parkinsonin tauti, Reaaliaikainen data, Digitaalinen biomarkkeri, Digitaalinen terapia

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Abbreviations

CBT	cognitive behavioural therapy
CP	chronic pain
DTx	digital therapeutics
ePRO	electronic patient reported outcome
ML	machine learning
ND	neurological disorder
NRS	numerical rating scale
QoL	quality of life
PD	Parkinson’s disease
RWD	real-world data
TSK	Tampa scale for kinesiophobia
UPDRS	unified Parkinson's disease rating scale
VAS	visual analogue scale
VR	virtual reality

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Tommi Gröhn*, Sammeli Liikkanen*, Teppo Huttunen, Mika Mäkinen, Pasi Liljeberg, and Pekka Marttinen. 2023. Quantifying Movement Behavior of Chronic Low Back Pain Patients in Virtual Reality. ACM Trans. Comput. Healthcare 4, 2, Article 11 (April 2023), 24 pages. https://doi.org/10.1145/3582487

II Eccleston, C., Fisher, E., Liikkanen, S., Sarapohja, T., Stenfors, C., Jääskeläinen, S. K., Rice, A. S. C., Mattila, L., Blom, T., & Bratty, J. R. (2022). A prospective, double-blind, pilot, randomized, controlled trial of an "embodied" virtual reality intervention for adults with low back pain. Pain, 163(9), 1700-1715. doi: https://doi.org/10.1097/j.pain.0000000000002617

III Liikkanen S, Mäkinen M, Huttunen T, Sarapohja T, Stenfors C, Eccleston C. Body movement as a biomarker for use in chronic pain rehabilitation: An embedded analysis of an RCT of a virtual reality solution for adults with chronic pain. Front Pain Res (Lausanne). 2022;3:1085791. Published 2022 Dec 20. https://doi.org/10.3389/fpain.2022.1085791

IV Liikkanen S, Sinkkonen J, Suorsa J, Kaasinen V, Pekkonen E, Kärppä M, et al. (2023) Feasibility and patient acceptability of a commercially available wearable and a smart phone application in identification of motor states in Parkinson's disease. PLOS Digit Health 2(4): e0000225. https://doi.org/10.1371/journal.pdig.0000225

1 Introduction

Healthcare is one of the most promising areas for the implementation of emerging digital technologies such as mobile devices, wearable sensors, artificial intelligence, and virtual reality. The definition *Digital Health* is still ambiguous, though FDA's definition includes categories of mobile health (mHealth), health information technology (IT), wearable devices, telehealth and telemedicine, and personalized medicine in it (Fatehi et al., 2020). Healthcare is increasingly exploiting these technologies, as they offer and enable new opportunities for diagnosis, monitoring, and treatment in different diseases. Despite these technologies have been efficiently exploited in various indication areas such as diabetes and oncology, they are outstandingly important in the field of neurological disorders (ND), such as Parkinson's disease (PD), chronic pain (CP), migraine, multiple sclerosis (MS), dementia, and Alzheimer's disease (AD), where use of non-invasive biological biomarkers for patient monitoring and drug development is challenging (Parnetti et al., 2019; Rejula et al., 2021). Due to the very subjective nature of these diseases (e.g., aetiology, onset, progression, symptoms), and because a direct measurement of the biological functionality of central nervous system, such as brain, is very difficult, especially remotely, indirect surrogate measurements are in many cases the only viable or possible option. This thesis is focused on CP and PD due to parallel development programs for Digital Therapeutics (DTx) solutions in these diseases.

Using different wearables, sensors, and mobile devices can help in the treatment of PD (Metta et al., 2021). As it is a chronic disease with a subjective progression and manifestation, the continuous optimisation of the treatment for an individual is challenging, especially when healthcare professionals in many cases meet patients once or twice a year (Pirtošek et al., 2020; Willis et al., 2011). Although the regulatory framework for digital health solutions is still not very mature, and the commercial viability is challenging, COVID-19 pandemic has highlighted the benefits of these as the access to healthcare resources has been difficult or even restricted (Hassan et al., 2020). Various electronic patient reported outcome (ePRO) tools have been developed to increase the compliance in the tracking of symptoms and medication, but these tools are an extra burden to patients, and they are a constant reminder to patients about their condition (Aiyegbusi, 2020; Ancker et al., 2015).

Continuous and passive monitoring of symptoms in people with PD may help in monitoring the treatment progression, measuring the treatment efficacy and safety, and offering the opportunity to automate the therapeutic regimens in the future (Battista & Romaniello, 2020).

Measuring CP and the effect of pain treatments continues to be a challenge for healthcare. Visual analogue scale (VAS) scoring systems and ePRO tools are widely used. The challenge is that both these methods are subjective, which means it is difficult for healthcare professionals to assess the situation objectively. Furthermore as with PD, asking constantly about the illness is not something that patients wish for (Healy, 2019). Continuous, automated, and more objective methods is thus an unmet need, and novel methods are constantly being developed (Kelly et al., 2011; Koskimäki et al., 2017; Storm, 2008; Verbunt et al., 2009).

Different sensors and wearables are used to collect relevant biosignals, both in controlled environment and from the real world. Similarly mobile devices are used to collect patient reported data. Sensor data collected from the real world is usually noisy, complex and the datasets tend to become rather large compared to laboratory measurements. Thus, in many cases analyses and predictions from this data require using novel data science methodologies such as machine learning in its various forms. When properly analysed, this process can be transformed into novel digital biomarkers (Chan et al., 2022; Dillenseger et al., 2021). Furthermore, when validated, these biomarkers can eventually be used as clinically validated endpoints in monitoring the progression of diseases and in measuring the effect of therapeutic interventions (Dillenseger et al., 2021; Piau et al., 2019; Stephenson et al., 2021; Vaarala et al., 2023). The opportunity of having digital biomarkers as validated endpoints exist in both more traditional drug therapeutics, and especially so with DTx solutions.

The definition of ‘a digital biomarker’ is not yet globally standardised. A definition of *“objective, quantifiable, physiological, and behavioral data that are collected and measured by means of digital devices, such as embedded environmental sensors or wearables*” has been used in several review articles (Babrak et al., 2019; Piau et al., 2019). This also fits with how data from sensors, wearables and mobile devices is aimed to be studied in this thesis. The attempt to develop clinically meaningful and credible digital measurements in PD and CP have many similarities, as both diseases are chronic and subjective by their manifestations (Morgan & Anghelescu, 2017; Rutten et al., 2021). It must be remebered though that PD and CP are two very different indications, and for instance PD is still not curable illness whereas CP in many cases is. Furthermore, often CP can be perceived as a symptom instead of a disease.

2 Review of the Literature

2.1 Chronic pain

About one in five people suffer from CP. It is defined as pain that persists or recurs for more than 3 months (Treede et al., 2019). CP usually consists of different and individual neurobiological, psychological, and social factors. It is associated also with multiple severe comorbidities such as depression, anxiety, sleep disturbances, fatigue, and neurocognitive changes (Fishbain et al., 2007; Gatchel et al., 2007; Macfarlane et al., 2001). CP can be alleviated with medicines, but often they are not able to solve the underlying problems, and may also have severe side effects, and can lead to unwanted situations such as the misuse of opioids (Eccleston et al., 2017; Jamison et al., 2010; Reibel et al., 2001). With CP, the body keeps sending pain signals to brain, even years after the injury is not anymore present (Treede et al., 2019). CP often has a negative impact on mobility, flexibility, strength, and endurance, which consequently may make everyday tasks and activities more difficult. As the existing medications do not work optimally or at all for certain patients, or have unwanted outcomes, there is a huge global unmet need for new and more efficient and usable therapies and treatments. CBT is a non-pharmacological option to those with chronic pain indications, but there are simply not enough therapists in the world to treat all those in a need. One option to alleviate this capacity problem is to exploit digital health in trying to upscale and digitalise the limited healthcare resources (Eccleston et al., 2020).

2.1.1 Measuring chronic pain

Measuring pain and the effect of the pain treatment has always been a challenge for healthcare. Novel methods of measuring pain and patient's ability to manage his/her everyday life objectively and passively are widely needed (Kelly et al., 2011; Koskimäki et al., 2017; Verbunt et al., 2009). It is difficult to compare the perceived pain of a person to the perception of another person. Various self-reported scales such as VAS, numerical rating scales (NRS), verbal rating scales (VRS), and faces pain scales-revised (FPS-R) have been used broadly (Lee et al., 2022; Thong et al., 2018). These approaches are not only subjective but are also forcing the focus of

patients repeatedly back to the disease itself, which is exactly the opposite the patient wants to achieve (Healy, 2019).

There are several imaging techniques like magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) that are used to measure relevant brain signals from patients in CP, but these are challenging to perform and interpret, need special equipment and expertise, and are also expensive measurements to be used in daily practise (Davis et al., 2012; Li et al., 2022; Specht, 2020; Witjes et al., 2021; Yoon et al., 2021). Also, the analysis of the movement and the facial expression images have been researched and exploited in the treatment of both in acute and chronic pain (Biebl et al., 2021; Priebe et al., 2020; Prkachin & Solomon, 2008).

Various neurophysiological tests can also be used in the assessment of CP. These tests can assess the functionality, or the lack of functionality, in the somatosensory pathways. Tests such as quantitative sensory test (QST), autonomic test, microneurography (MCNG), laser evoked potentials (LEPs) and contact heat evoked potential stimulator (CHEPS) are widely used and developed in the field of pain research (Evdokimov et al., 2019; Jääskeläinen, 2017; Janner et al., 2018; Merkies et al., 2015; Provencher et al., 2021; Zafereo et al., 2022). Two interesting methods that are currently being researched also in the assessment of CP are transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (tACS) (Ahn et al., 2019; Simis et al., 2021). The hypothesis behind these methods is that large-scale electrical brain activity patterns in the thalamocortical system plays a key role in the pathophysiology of CP (Ahn et al., 2019). Some of these neurophysiological tests are however invasive and many of them require specific test systems and trained users to perform the assessment (Johnstone & Frank, 1995). They are thus not suitable for remote assessment.

One option is to measure the consequences of CP over the time, instead of the actual sensation. In the case of kinesiophobia, the fear of movement, The Tampa Scale for Kinesiophobia (TSK) is a common and globally accepted scale for the assessment (French et al., 2007; Gómez-Pérez et al., 2011). The limitations of this kind of method and scale are of course the same as with any of the direct pain scales. Thus, the aims to monitor the consequences of CP such as physical activity, heart rate, gait and sleep have been researched (Aqajari et al., 2021; Skogberg et al., 2022; Zheng et al., 2022).

2.2 Parkinson's disease

PD is a common neurological and neurodegenerative disorder. Its prevalence is 1–2 per 1000 persons, increasing with age (Tysnes & Storstein, 2017). The disease primarily affects dopaminergic neurons in a specific brain area, substantia nigra,

leading to motor symptoms (Kalia & Lang, 2015). Currently the patients are treated by alleviating their symptoms by e.g., levodopa medication or deep brain stimulation (DBS) devices (Bloem et al., 2021). In many cases finding the optimal medication dosing can be challenging and by the time when PD advances, these often offer the patients only a temporary solution. A major challenge is that many patients start experiencing the fluctuation of PD symptoms through the day, known as OFF periods (Sivanandy et al., 2021). These can occur both as motor and non-motor symptoms, and sometimes, they can disrupt the rest of day despite medication compliance. As disease-modifying treatments are still waiting to be discovered, understanding the subjective nature of the disease and how the person perceives his/her symptoms, as well as how these are associated with the current therapies in PD, is vital to effectively personalise and optimise the treatment.

2.2.1 Motor symptoms

The most common PD medicines are aimed to minimise symptoms, such as, tremor, bradykinesia, rigidity, postural instability, and dyskinesia, the latter caused by the dopamine-increasing medication such as levodopa. Understanding these symptoms as well as their association to the treatment is vital to effectively personalise the therapy.

Objective quantification is essential to determine the severity of a symptom, and to evaluate responses to treatment. This can be done with electromyography (EMG) sensors (Rissanen et al., 2021; Rissanen et al., 2015) or accelerometers (Ayturk et al., 2017; Goetz et al., 2008; Hallett, 2012; Isaacson et al., 2019) by detecting the frequency, direction, and amplitude in the resting and/or moving state.

In various clinical studies, laboratory-grade accelerometers have been successfully used to assess tremor and to quantify the treatment effects (Brennan et al., 2002; de Haas et al., 2011; Maetzler et al., 2016). Recently, accelerometers in consumer products such as smartphones, smartwatches and activity meters have enabled easy-to-use domestic measurements. These may provide a cost-effective and user-friendly alternative for laboratory measurements (Kostikis et al., 2015; Kulisevsky et al., 1995; Schreglmann et al., 2018). It has to remembered that access to the raw sensor data is important as different manufacturers analyse the accelerometer data in various ways. Several studies have already been performed with iOS and Android platforms to measure tremor in patients with PD. These are shown to be good enough compared to laboratory-grade accelerometers and electromyography devices (Fraiwan et al., 2016; Goetz et al., 2004; Joundi et al., 2011; van Brummelen et al., 2020).

2.2.2 Non-motor symptoms

In many cases PD patients suffer also from non-motoric symptoms such as sleep disorders, anxiety, chronic pain, and hallucinations (Bannister et al., 2021; Erb et al., 2020; Sringean et al., 2016). As the assessment of the severity of the disease is traditionally made by a physician performing various clinical tests, the outcome has low resolution and is also relatively subjective to a physician, but it also misses the non-motoric symptoms. These need to be assessed by either interviewing the patient or by using ePRO tools which in practise means patients filling in electronic diaries and questionnaires. The use of ePRO tools creates partially insufficient and inaccurate data as the patient do not record the incidents while they are occurring (Erb et al., 2020; Oleksandr Sverdlov et al., 2018). Thus, there seems to be a significant opportunity for objective, high-resolution, continuous monitoring afforded by wearable technology to improve upon the monitoring of PD symptoms.

Detecting a non-motoric symptom is much more difficult than measuring motoric symptoms. However some of the non-motoric symptoms can be measured indirectly, like the quality of sleep (Sringean et al., 2016) and heart rate variability by using heart rate (HR) sensors (Zawadka-Kunikowska et al., 2017). In a review study (Heimrich et al., 2021) over 47 studies with 2772 PD patients a strong decrease in parasympathetically modulated heart rate variability (HRV) parameters compared to healthy controls was found. Lower values of high frequency component (HF) and root mean square of successive heartbeat interval differences (RMSSD) were found during short-term measurements in the PD meta-cohort.

2.2.3 Other patient reported outcomes

As explained earlier, ePRO tools and similar proprietary techniques such as mobile apps are widely used in the collection of motor and non-motor symptoms by querying input from subjects by pre-defined forms such as PRO-PD and unified Parkinson's disease rating scale (UPDRS) (Martínez-Martín et al., 2015; Mischley et al., 2017). These tools can also be used in the collection of other valuable data and insights from subjects. Mobile devices have also been exploited by transforming selected parts of MDS-UPDRS III (motor subscale) tests into electronically performed, self-administered tasks, such as finger tapping, hand pronation-supination and reaction time tasks ((Mitsi et al., 2017; Wissel et al., 2017).

Quality of life (QoL) scales such as PDQ-39 and PROMIS-10 assesses how often people with Parkinson's experience difficulties in daily living, and currently one can use them either in paper or electronic format (Morley et al., 2014). More and more both regulators but also those making decisions on reimbursement see value in this data. Furthermore, these data collected with scales such as PDQ-39 can be used in both optimising and measuring the performance of algorithms (Zahra et al., 2020).

2.2.4 Data science in symptom detection

The development of algorithms for more objective and automated evaluation of symptoms has been going on for several decades (Albers et al., 1973). Until the new era of artificial intelligence (AI) and machine learning (ML), the methods were traditional statistical and frequency domain analysis methods. For instance frequency power spectrum was found to have correlation between selected spectral features and dyskinesia (Burkhard et al., 1999). Different regression and analysis of variance (ANOVA) models have also been used successfully in (Kleinholdermann et al., 2021; Toosizadeh et al., 2015) the detection of PD symptoms.

The possibility to collect data with novel sensors and wearables at home settings instead of laboratory grade sensors and settings has increased the complexity and size of datasets. Furthermore, these datasets are noisier. Also, as PD symptoms are subjective, and even culturally dependant, understanding these symptoms with wearables by combining sensor data with both the patient's and physicians' assessments is not something that can be easily solved by using traditional analytical methods (Kaasinen et al., 2023). Thus, the application of different ML techniques alongside with the increasing access of high-performance computing assets has increased over the recent years (Chicco, 2017). Several non-neural and neural network methods have been successfully used to detect PD symptoms from sensor data (Aich et al., 2020; F. M. J. Pfister et al., 2020).

So far algorithms have been developed mainly by using the physician's assessment as UPDRS as the source of labelling of the sensor data (Hadley et al., 2021; Khodakarami et al., 2021; Krause et al., 2021; F. M. J. Pfister et al., 2020; Um et al., 2017). Overall, there seems to be very little research done on algorithms that would be optimised by using patient's own perception of symptoms as the labelling element. Furthermore, there is still a need to understand further how much, and what kind of data needs to be collected and from how many patients to get algorithms with sufficient sensitivity, specificity and accuracy for clinical purposes.

2.3 New modality of Digital Therapeutics

Digital therapeutics (DTx) is novel treatment modality (O. Sverdlov et al., 2018). Even the DTx is only less than a decade old. DTx solutions are clinically validated efficacious and safe software interventions to treat, manage, and prevent a broad spectrum of diseases and disorders such as diabetes, depression, pain, and various neurological disorders. In many cases DTx solutions are used together with other treatment interventions and medications. Regulatorily they are classified by EU medical device regulation (MDR) as medical device software (MDSW) and by US Food and Drug Administration (FDA) as software as medical devices (SaMD).

2.3.1 Virtual reality (VR) in the treatment of pain

Because of its immersive nature VR has been found to be an effective way to distract pain for a short period of time during an acute pain episode (Hoffman et al., 2020; Hoffman et al., 2001). This distraction mechanism has been widely explored and is used in many existing or developing VR solutions in healthcare and there seems to be common conclusion that with acute pain it works. As an example, Oncomfort is used to digitally sedate patients during surgical operations through hypnosis, without having to use any traditional sedatives (Rousseaux et al., 2020). As counter intuitive as it may sound, they have already gained experience from surgical operations (Moon et al., 2018).

VR can in many cases alleviate pain without severe treatment related adverse events. The device related problems such as nausea have disappeared by the improved screen refresh rate, though e.g., VR is still an issue with people having epilepsy (Fisher et al., 2022). As the CP medications have often challenging safety concerns, VR has been explored in the treatment of CP (Tack, 2021). Chronic pain is more complicated indication than to treat than acute pain as it has individual neurobiological, psychological, and social factors. The distraction seems be a way to alleviate the pain for short period but in the longer run the efficacy won't last (Mallari et al., 2019). As a result, distraction is still exploited in CP treatment, but other techniques such as neuromodulation and graded exposure therapy are researched to be used as part of the treatment (Garcia, Birckhead, Krishnamurthy, Sackman, et al., 2021; Solcà et al., 2021; Tack, 2021). As expected, when well designed, VR based treatments do seem to be potential in CP, at least as a complementary treatment, and the efficacy also is shown to last for at least several months (Garcia, Birckhead, Krishnamurthy, Mackey, et al., 2021; Garcia, Birckhead, Krishnamurthy, Sackman, et al., 2021; Goudman et al., 2022). More research is still needed to understand how permanent the efficacy of VR based treatments is. Likely this will be dependent on the solution and its target population.

As a result, there are several DTx solutions being developed for CP indications. One of the more advanced is Motion Coach app by Kaia Health, which uses image recognition technique in the physical exercise therapy in low back pain patients (Biebl et al., 2021; Toelle et al., 2019). AppliedVR is developing a VR based DTx cognitive behavioural therapy (CBT) solution for chronic low back pain (CLBP) patients (Garcia, Birckhead, Krishnamurthy, Mackey, et al., 2021), and their brand EaseVRx was granted a breakthrough device designation by US FDA late 2021. BehaVR has also designed a DTx treatment for the same target population, however their treatment is still categorised as well-being solution. AppliedVR's approach also uses VR's immersive nature in distraction for CLBP patients, by creating the user various distractive techniques like games and mindfulness exercises.

In CP the long-lasting situation is however more complicated and not restricted to the pain, but in many cases to the consequential problems such as lower level of activity, inability to work, sleep disorders, reduces social life and even decreased cognitional ability. One of the most difficult consequences in CP is kinesiophobia (Picavet et al., 2002). It can be effectively treated with CBT, aiming to change how people perceive and behave when facing the fear of movement in CP (Eccleston et al., 2022; van Hooff et al., 2021; Zhang et al., 2020). Examples of VR environments from ROHKEA™ (ODD-403) solution, aimed to treat kinesiophobia in CLBP patients can be seen in **Figure 1** and **Figure 2**.

Figure 1. Example of an immersive VR environment from ROHKEA™ (ODD-403) by Orion Corporation, a solution aimed to help CLBP patients suffering from kinesiophobia: ”home cabin” that begins each intervention day.

Figure 2. Example of an immersive VR environment from ROHKEA™ (ODD-403) by Orion Corporation, a solution aimed to help CLBP patients suffering from kinesiophobia: three environments in where the exercises are performed (“creativity garden”, “fabrication forest” and “power mountain”).

There is evidence that hippocampus plays a role in emotional processing, including facilitation of fear, anxiety, and avoidance behaviours (Mizuno et al., 2020; Perry et al., 2011). There is also some early evidence from experimental animal studies to suggest that when using VR, the hippocampus area activity becomes partially occupied (Ravassard et al., 2013). The research on this still very modest, but if true, and VR would impact hippocampus also with humans, it might enable the use of VR in activating new behavioural patterns – neural connections – in patients. Thus, manipulating the hippocampus with VR might enhance new behavioural changes as part of the CBT treatment process. Some small pilot studies have also been done to support this hypothesis (Tong et al., 2015). On the other hand, the role of amygdala in the control of emotions such as anxiety, when facing sensory stimulus is well known fact. Thus, creating artificial sensory auditory and visual stimulus by VR immersion, which is then stored into memory via hippocampus could also favour the use of VR in the well-designed CBT programs.

Immersive nature is of course not the only opportunity in developing novel VR based CBT treatments. Using VR enables self-treatment at home which can improve the access to treatment for more people without increasing the costs (Shin et al., 2021). This also means possibility to monitor and even adjust the treatment remotely, which is not only a pharmacoeconomic opportunity, but also an opportunity in the actual treatment dynamics (Ma et al., 2021). Furthermore, the programmable nature of virtual environment enables using more personalised and localised treatments (Baños et al., 2009; Shiban et al., 2013). Some selected opportunities are listed in **Table 1**.

Table 1. Selected opportunities of VR in the CBT.

Benefit	Rationale	Reference
Immersive and realistic experience elicits empathy and physiological responses	VR impacts directly to brain areas connected to emotions such as fear of movement related to CP	(Ravassard et al., 2013; Tong et al., 2015)
Lasting hyper engagement of subject matter	Reskilling through experiential learning and spaced repetition in VR	(Hood et al., 2021; Pedram et al., 2020)
Minor adverse effects	Motion sickness and photosensitivity are minor adverse effects compared to the ones with pharmaceutical medications e.g. opioids	(Kim et al., 2018; Tychsen & Thio, 2020)
Scalability of CBT treatment	Traditional CBT can be supported by self-treatment sessions CBT Self-treatment can be administered anywhere at anytime	(Donker et al., 2019; Navarro-Haro et al., 2019)
Personalised treatment	Adjustable VR environment Continuous measurement within and between the treatment sessions Adjusting the treatment sessions based on measurements	(Baños et al., 2009; Shiban et al., 2013)
Suitable therapy to at any stage of the condition	Possibility for psychological interventions throughout the patient journey in various indications	(Flores et al., 2018; Garcia, Birckhead, Krishnamurthy, Sackman, et al., 2021)

2.3.2 Remote monitoring in the focus for PD

The development of DTx solutions in PD is concentrated in the diagnose and remote monitoring purposes (Ellis & Earhart, 2021). There are still only a handful of interesting DTx treatment solutions being developed for PD. MedRhythms is developing a solution to improve walking outcomes based rhythmic auditory stimulation (RAS) (Ellis & Earhart, 2021). As promising as it is, it still might require a broader offering of services around it to be useful for the users. It is still a very potential opportunity for digital biomarkers, and even for a digital endpoint though. Neptune by Orbit Health is another interesting platform which aims to harness the power of wearables and AI to improve and optimise the current treatment practises (Franz M. J. Pfister et al., 2020), though it is very healthcare centric by its design. Rune Labs uses Apple Watch in the remote monitoring of PD symptoms, also in collaboration with Medtronic DBS devices (Pathak et al., 2021). The need to use the Apple Watch might be an obstacle here because of price and usability challenges.

The rest of the DTx solutions are mainly concentrating on a specific method or a hardware wearable in collecting diagnostic data for the purpose of treatment management (Guan et al., 2021; Isaacson et al., 2019). The patients themselves are not yet in the epicentre of the design of most of these services - they seem to be more technologically designed for the healthcare processes than human centric solutions for the users.

2.4 Usability in real world data (RWD) collection

The use of digital tools in healthcare are becoming more common in assisting people in independent living and self-management of illnesses. With the aging population, this might also help us in battling against the increasing healthcare costs, though health economics evidence is still not very clear (Gentili et al., 2022; Gonçalves-Bradley et al., 2020).

Digital tools will be beneficial for several disease populations only if they are designed to match with the specific needs, wishes and personal characteristics of the aging individuals (Turesson et al., 2022; Wildenbos et al., 2019). The usability of digital tools in PD and CP patients have been studied and it seems that also these patients are willing to use novel technologies in their everyday life only if these have been designed to be compatible with their specific needs and abilities (121, 122). Otherwise, the usability in a certain target population with special needs (e.g., ability to use complicated devices) will be low, and the users are not able or motivated to use the tools and solutions. I find this aspect often neglected by the developers who are in many cases young and technically very capable themselves. Thus, the age, gender and technical abilities among other possible variables is the part we need to take into consideration when designing good user and patient experience (Imbesi et al., 2022; Wildenbos et al., 2019).

Understanding the different intrinsic (e.g., disease related usability challenges) and environmental attributes and barriers (e.g., access to mobile network) is the first step in designing a usable digital experience for different use cases (Biduski et al., 2020; Wildenbos et al., 2019). Usually this involves qualitive research of target population and the relevant stakeholders (e.g., caregivers and healthcare providers) before designing the solution (Walker et al., 2019).

We should clearly focus more on the individuals behind the disease, instead of the disease, itself when designing digital solutions for them.

3 Aims

The aim was to study the usability and feasibility of real-world data (RWD) from wearables, mobile devices, and patients in exploring digital biomarkers and endpoints for therapeutic purposes in two ND indications: CP and PD. These diseases offer interesting research use cases for RWD solutions. The aetiology for ND illnesses (such as CP and PD) is often not fully known and the diagnosis of the state of the disease, and especially its progression is sometimes challenging or difficult to predict. In many cases the overall assessment of the disease progression is mainly based on the physician's assessment in the clinic. More objective, non-invasive and direct measurements are lacking and there is a clear unmet need to understand what the patient is experiencing in the real life.

The key hypothesis of this thesis is that by using commercially available wearables and mobile devices with patients in real world allows us to measure, analyse and detect clinically valid digital signals. These could be used as digital biomarkers in the future and thus be used as clinically validated endpoints in:

1. diagnosing ND at early stages,
2. monitoring the progression of ND and
3. measuring the effect of therapeutic interventions, both with traditional drug therapeutics and with DTx interventions.

4 Materials and Methods

4.1 Study subjects (I-IV)

The laboratory grade wearable dataset in CP was collected from CLBP patients (n = 10) and healthy volunteers (n = 10) in a VIRE study by using a specifically designed VR program, Painlab. The study was performed in the clinical research unit at Orion Corporation, Espoo, Finland. The inclusion criteria for participants were:

- CLBP for at least 3 months (the most painful condition should be low back pain).
- Ambulatory
- Average pain intensity of ≥ 4 over the past week on a 0 − 10 NRS, either at rest or on back-extension movement.
- Oswestry Disability Index of ≥ 26%
- Medium (34-41) or high TSK score (42-68).
- Can stoop without severe pain.

Nine out of ten patients were females. Accordingly, four out of ten controls were females. The average age of the patients was 55 (SD = 7.3), and of the controls 35 (SD = 6.3). However, the age difference does not explain the results.

The RWD in CP was collected as part of the VIRPI study (registered on ClinicalTrials.gov: NCT04225884). Adults with CLBP were recruited, screened, and then randomly allocated to one of the study arms. Participants and study personnel were blind to allocation. Data from study arms were used in data analysis as follows:

- Movement data from DTxP arm (N = 12)
- EDA from DTxP and Sham Placebo arms (N = 29)
- Activity data from DTxP, Sham Placebo and Standard Care arms (N = 39).

39 participants, of which 34 were women, were randomized. All were adults with an average age of 54.7 years. 30 participants reported more than 5 years of low back

pain. The mean pain intensity on a scale of 0-5 at the start of trial was 2.8. Mean Oswestry Disability Index (ODI) was 36.1 (range 18-60), which means high level of disability in the study population. Similarly, mean reported TSK was 41.8 (range 29-55), meaning a strong belief that movement would lead to further pain and reinjury.

The laboratory grade wearable dataset in PD was obtained from Michael J. Fox Foundation (MJFF) Levodopa Response Study (Daneault et al., 2021). It contained data from two different clinical sites in US (Boston and NYC) collected in a study which aimed to measure wearable data from 30 PD patients.

RWD in PD was collected by an open, non-randomized, data collection study DAISY. Inclusion criteria for the study participants were:

- the diagnostic criteria for PD (Postuma et al., 2015)
- on-going Levodopa (LD) treatment
- a history of motor fluctuations, i.e., daily LD-treatment related changes in the severity of tremor, bradykinesia and/or rigidity.

The participants were recruited at outpatient clinics of Helsinki University Hospital, Oulu University Hospital and Turku University Hospital. Spouses of the PD patients, free of any ND, were recruited as control subjects to get wearable data from similar circumstances but without any PD symptoms in it. The dataset consisted of data from 65 participants (42 subjects with PD and 23 control subjects without PD). Six participants had DBS devices. Of these, 3 participants with PD had little to no RWD to be used in the analysis because of premature discontinuation (2 subjects) or technical data transfer issues (1 subject) and the data from these subjects was not used in analyses.

4.2 Study designs (I-IV)

The approach (**Figure 3**) with both indications was similar. First, a reference wearable dataset collected in the laboratory settings (VIRE study and dataset obtained from Michael J. Fox Foundation) was studied by using exploratory methods to enable the development of a suitable analytical method for the RWD. This was done to be able to study the characteristics of the wearable data in the question in a less noisy and more homogenous data. Later, the analysis of the real-world wearable dataset (VIRPI and DAISY studies) was performed by using the learnings with the laboratory grade wearable data. In both cases the population size in laboratory grade dataset was smaller than in the RWD.

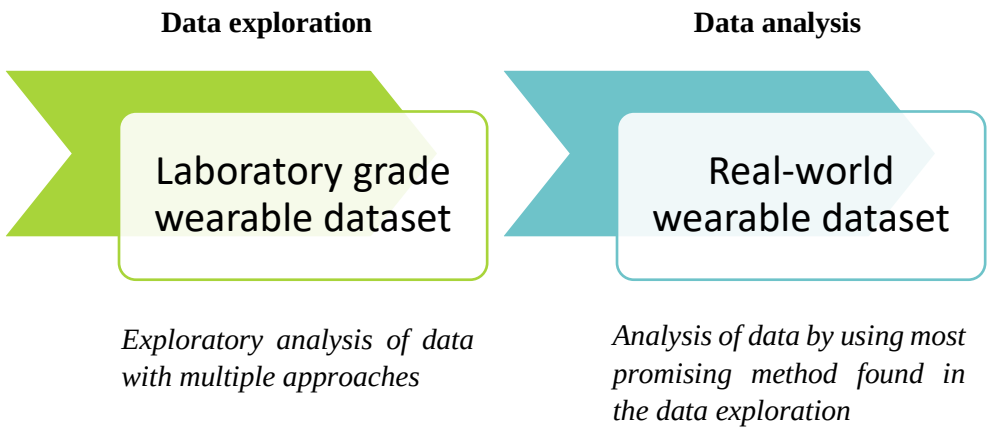

Figure 3. The study design for the analysis of real-world wearable dataset with the help of laboratory grade dataset

The VIRE study was open-label feasibility study.

The VIRPI study design (**Figure 4**) was a double blind three-arm prospective, double-blind, randomized controlled trial comparing a digital therapeutics software solution for CP (DTxP), a Sham placebo comparator, both against standard care (Eccleston et al., 2022).

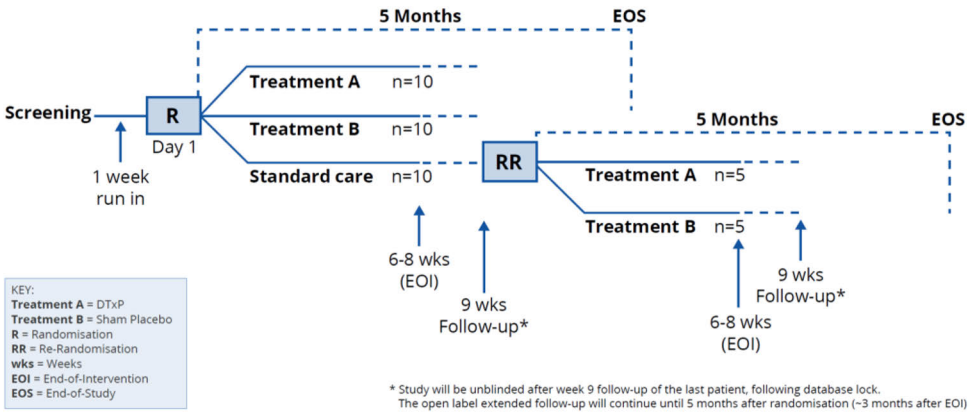

Figure 4. The design of VIRPI study

The DAISY study consisted of screening and training visit, a roughly four weeks long data collection phase with two intensive periods in it, and an end-of study visit. The study design is presented in **Figure 5**.

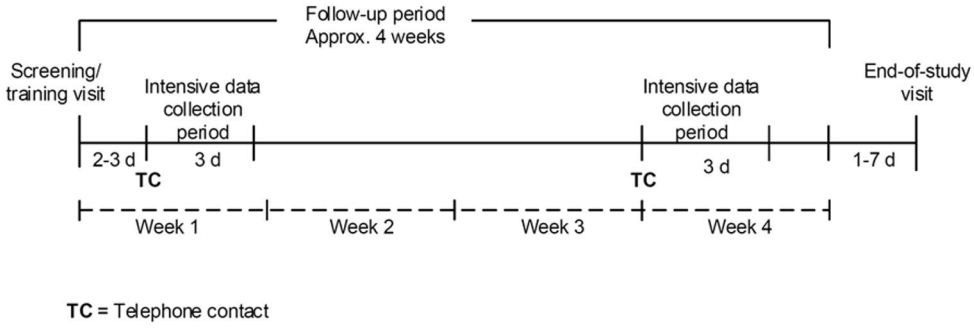

Figure 5. The design of DAISY study.

4.3 Assessment of pain with CLBP (I-III)

The VIRE study participants were screened and examined. Basic demographic variables, The Keele STarT Back Screening Tool, Pain interference Short Form 3a, Pain interference Short Form 6b, Pain NRS, TSK, Oswestry Disability Index (ODI) and Familiarity with digital devices assessments were collected in the beginning of the study visit. TSK, Game Experience Questionnaire (GEQ) and Modified Game Experience Questionnaire (Modified GEQ) assessments were collected one week after the study visit.

The movement data were collected when using a specifically designed VR software, Painlab. It was coded with Unity v2019.3.7f1 and used by commercial OCULUS Quest and Touch VR headset and hand-held controllers. VR environment was run at a refresh rate minimum of 70Hz. The sensor data were collected by using built-in sensors in headset and hand-held controllers. The movement data was collected at 30Hz rate.

All participants were asked to perform the exact same set of specific movements in VR environment. The movements were designed to mimic real-life tasks and the movements that CLBP patients might avoid. This was done to maximize the generalizability of the data-analysis to other similar kind of movements in the real-life. All together there were four movement patterns for both hands, each pattern consisting of three movements. The first four patterns were done with the right hand and then the same patterns were done with the left hand.

The participants were requested to do a series of certain pre-designed tasks in VR (see **Figure 6** as a scheme of a task). The movements, designed together with physiotherapists and pain experts, were based on a VR treatment that was used in VIRPI study with CLBP patients (Eccleston et al., 2022).

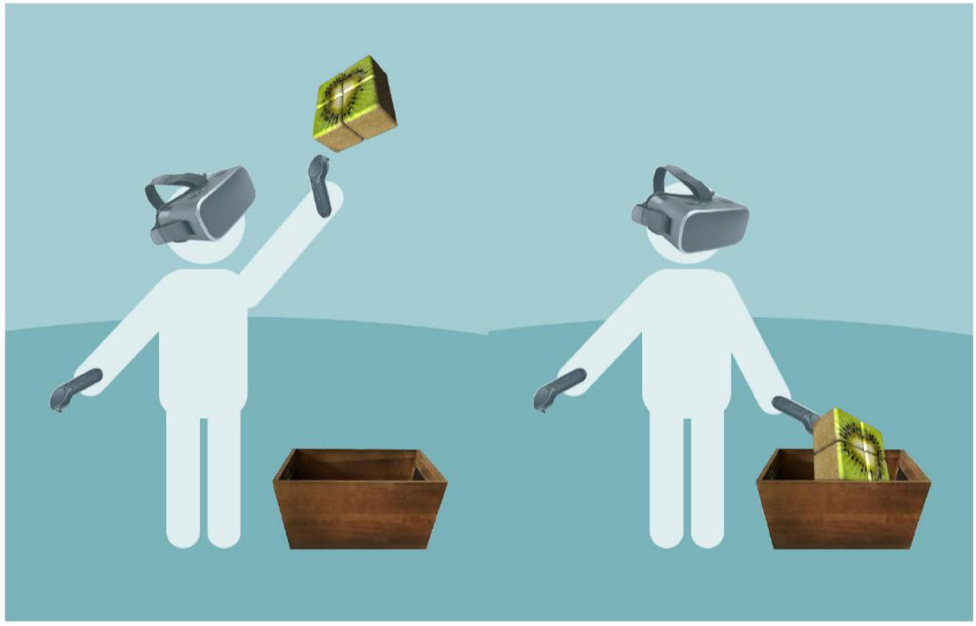

Figure 6. A scheme of a movement within a pattern: the user grabs an object located above on the left side with left hand, and then puts it in a box which is located next to the user.

As illustrated in **Figure 6**, the movements consisted of a user grabbing an object from various 3D locations and then putting the object into a box in the VR environment. The location of the box remained fixed (in front of the user) but the location of the object varied as follows:

- in front of user
- above on the right side
- above on the left side
- on the right side
- below and behind
- below on the right side
- behind the user
- on the left side
- below on the left side
- above on the left side.

In the VIRPI study, the DTxP arm was a VR based treatment program consisting of 24 individual intervention days in a virtual environment with a typical Nordic cabin, a garden, and lakeshore. All 28 intervention days were meant to be executed within 6-8 weeks from the start. The program had behavior change content, provided by a virtual mentor with audio and subtitles, and gamified tasks designed together with Finnish physiotherapists. All intervention days began in a cabin like VR environment (**Figure 7**), which after garden and lakeshore environments were used to run other exercises.

Figure 7. Example from VR environment in VIRPI study: “the cabin” which begins every intervention day

The program contained psychological content and various gamified physical, psychological, and cognitive exercises. Exercises were designed to facilitate and improve specific movements, typically avoided by low back pain patients (see **Figure 8** as an example).

Figure 8. Example from VR environment in VIRPI study: “gamified physical and cognitive activity exercise” where the user was performing various tasks and puzzles with geometric objects as fruits

The Sham placebo was as exactly as the DTxP but without any behavior change or active content. The arm was designed to see e.g., what kind of impact the VR immersion itself has, even without any CBT or exercise content in it (Sedgwick & Hooper, 2015). Furthermore, it was assumed that relaxation in VR environment itself might have an effect.

DTxP (n = 12) and Sham placebo (n = 17) participants received Oculus Quest VR head mounted device (HMD) and handheld controllers. 10 participants were allocated to the standard care arm. All participants (n = 39) were given Empatica Embrace2 and Garmin Vivosmart4 wearables, and a mobile phone for transferring the data into a server. All participants were given applicable user instructions and training to use the devices. The wearables were configured not to show any data to participants.

As DTxP arm was the only that had content to promote moving. The Sham placebo arm in which the participants were instructed to relax in VR environment was assessed to have too limited amount of movement data relevant to this study. Thus, only the DTxP arm accelerometer data were collected (30Hz) when the participants were using VR devices. The software to collect the movement data was a bespoke by Unity development framework (v2019.4.18f1). The accelerometer data

were sent to a server via RESTful API calls. Data from the server were exported in JSON format, transformed into CSV files by SAS software, and analyzed by R software.

Empatica Embrace 2 electrodermal activity (EDA) data were collected throughout the whole study (4Hz).

All participants wore the Garmin device throughout the whole study to collect daily activity data. Aggregated data for heart rate, steps and sleep duration were downloaded from the Garmin server after the finalization of the study.

The following clinical endpoints were collected from all VIRPI participants:

- TSK for the fear of movement and re-injury had 17 items assessing beliefs about pain-related movement and possible further pain and reinjury using a 4-point Likert scale from strongly agree to strongly disagree. Higher scores meant higher fear of movement and re-injury.
- EuroQoL VAS for Overall Health condition from 0-100 with 0 being as ‘the worst health you can imagine’ and 100 as ‘the best health you can imagine’.
- EuroQoL-5D-5L for QoL to assess mobility, self-care, usual activities, pain/discomfort, and anxiety and depression from 1-5 (1 = no problems; 5 = unable to/extreme problems).

4.4 Assessment of symptoms in PD patients (IV)

The sensor data was in MJFF study were collected by using smartphone and smartwatch (GeneActiv, Pebble, phone, or Shimmer), with and without levodopa infusion ("drug state" in later discussion), while doing different tasks (**Table 2**), and it had some repetitions within the tasks. For each of these replicates, or combinations of the afore-mentioned variables, tremor, bradykinesia, and dyskinesia were scored by external observers onto an ordinal scale. Of all available data, only accelerations from the dominant hand, and the observer scores were used here.

Table 2. List of acronyms and tasks in the MJFF dataset

Acronym	Task
stndg	standing
wlkgs	walking straight
wlkgc	walking while counting
strsu	stairs up
strsd	stairs down
wlkgp	walking through a narrow passage
ftnd	finger to nose, dominant arm
ftnu	finger to nose, undominant
ramd	repeated arm movement, dominant
ramu	repeated arm movement, undominant
ststd	sit to stand
drawg	drawing and writing on a paper
typng	typing on a computer keyboard
ntblt	assembling nuts and bolts
drnkg	take a glass of water and drink
orgpa	organizing sheets in a folder
fldng	folding towel
sittg	sitting

In the DAISY study the investigators assessed baseline characteristics, Hoehn and Yahr stage, and Unified Parkinson's-disease rating scale (UPDRS parts I-IV) on the screening/training visit from participants with PD. This visit also included the training of study participants by the study nurse to the mobile app and the wearable.

All participants were given a Garmin Vivosmart® 4 wearable and a bespoke Android mobile application specifically designed and built for this this study. The application had three key functionalities:

1. a medication reminder for levodopa and other PD related medication intake,
2. a self-report of any motor or non-motor, both during the symptoms and/or retrospectively, and
3. an automatic transfer of the Garmin wearable data and patient reported data to server via mobile network. Both the wearable and the mobile app using the same clock server.

During the follow-up period wearable data were collected from all the participants throughout the whole period. Levodopa treatment intake and subjectively reported symptoms were collected with the application from subjects with PD. Participants reported symptoms as "bad moments" by pushing a specific button designed to be easily accessible within the front page of the mobile application. Once the symptom was over, the participant was accordingly able to end the symptom reporting by a similar button. Then participant was asked to classify the symptom by either choosing the correct one from a pre-defined list (**Table 3**), or as free text under the heading 'other'.

Table 3. List of pre-defined symptoms in the mobile application

Motor symptoms	**Non-motor symptoms**
Tremor	Sleeping disturbances
Rigidity	Anxiety
Slowness	Dizziness
Dyskinesia	Hallucination
Balance	Symptom of smelling or tasting
	Symptom of urination
	Symptom of digestion
	Pain

At the end-of-study visit, UPDRS II (Self-evaluation of activities of daily living) scale was assessed for the PD patients by the study nurse. In addition, a usability questionnaire was completed for all subjects by the study nurse who also interviewed the subject.

4.5 Statistical methods (I-IV)

The exploration with different analytical methods with the laboratory grade wearable movement data from VIRE study was divided into three stages: 1) feature selection, 2) times series segmentation using Hidden Markov method (HMM) and 3) classifying patients and healthy controls with logistic regression. In the first and second stages only the data from the left hand were used. The movement data between the left and right arm was too different to be used as one joint dataset here. However, in the third stage the data from both hands were combined as one dataset after normalising them into the same scale. This was done to maximise the size of the dataset.

To assess different features in the movement data, the distributions of features between the healthy and CP participants were compared against each other using box-and-whisker plots. The collection of data from two healthy participants when using the right hand was not successful and these were not used. The left-hand data were used as the training data (N = 20), and right-hand data as the test data (N = 18). The time to perform each pattern was calculated for all. It was assumed that healthy are moving their hand with higher speed compared to those with CP. Thus, the total variation of velocity was assumed to be bigger for them. This was calculated from the 3D velocity data, which was derived from the positional data. Also, the mean and the variance for the distance between the head and the active hand were calculated. Again, the mean values with healthy participants were assumed to be bigger than with CP participants.

Four different features were selected for classifying patients: the time, the total variation of velocity, the mean distance between the head and the active hand, and the variance of the distance between the active hand and head. A two-sample t-test was performed for each variable and the corresponding p-value.

Next the patterns of movements were segmented with HMM for further data analysis. The structure of these patterns was approximated with HMM by using standard expectation-maximization and forward-backward algorithms, thus HMMs did not need a lot of data to be trained. HMMs learned the sequence of hidden states by using 3D observations. In practise the found hidden states represented the parts of movements. For example, lifting the hand up might have been one part of a movement, followed by a movement to left as the second part. As the Painlab users performed movements in a predefined order, a left-to-right topology for hidden states was used.

After segmentation a visual check was done to understand which data type is the most promising for HMM segmentation. Three different data channels were given to HMMs: positional data, velocity, and normalized velocity. The number of hidden states was chosen by manual exploration during the method development. HMMs with 11 hidden states were used, and visually compared with each other. Other

amount hidden states could have been used but the differences around the used value (10 or 12) were not great. This was also confirmed when assessing the performance of the logistic regression models. However, when using too few (e.g., 3) or too many (e.g., 20) the segmentation was not useful. After plotting the segmented data, posterior predictive checking was performed for the HMM using normalized velocity data.

Finally, a classification of patients and controls with logistic regression was performed. The first logistic regression model was trained one by using non-segmented data. The chosen four features were calculated using the whole time series. The second model was trained by using segmented data. Here the features were calculated based on multiple segments created by HMM. The average predictive likelihood and accuracy were calculated for both models. The binomial test for classification accuracy was used to confirm that the results were significantly better than random, and to calculate the corresponding p-value. Lastly, the two logistic regression models were compared against each other by using four different selected parts of the movement dataset. To maximize the size of the test set, a leave-one-out cross-validation was used.

The movement data from VIRPI study were manually segmented using VIRPI software metadata on the software sequences that were run at each time point. However, the exact movement task information was not available, and available metadata contained just the information about the beginning and the ending of a program sequence (e.g., activity exercise). By using available metadata, the segments were manually classified as action and no-action. No-action segments were labelled “start of day”, “between” and “end of day”, depending on the relation to the action segments. As with the laboratory grade data analysis, the time was assumed to be a critical feature. The time spent on a given activity was assumed to correlate with the condition of a participant, meaning healthy users should finish the activities faster than users with CLBP. This hypothesis is also backed up by previous research in patients with CP, in both motor and problem-solving skill exercises (Kazim et al., 2022; Tsang et al., 2022; van Dillen et al., 2021; Zou et al., 2019). As the possibility to segment VIRPI data into specific movement tasks was not possible, the segment average velocity was used instead. Faster average velocity indicated finishing an activity faster.

Three-dimensional location data were collected from both hands and head mounted device in approximately every 0.03 seconds. These time-series data were then combined to segments of location data based on metadata. To analyze the movement data, the 3D location data were transformed into 3D velocity. Velocity in-times-series was then aggregated to the average velocity for every movement segment.

The distributions of velocity in action segments and no-action segments were compared visually. The data labeled as action were used in the movement data analysis. Linear regression lines were fitted to action velocity averages over the study to assess the overall progress, however this assessment can only be seen as a proxy for natural, as the diurnal aspect of regression is not naturally linear. Slope of this regression was assessed.

The correlations between the movement data changes in the sensors (Head, Left, Right) and in clinical assessments (TSK, Overall health VAS, EQ-5D-5L QoL score) were calculated. For sensors, the change was the slope of the regression line (the slope was multiplied by VR study days for a participant). For clinical assessments the change was the change from baseline at End of Treatment after 30 study days. The correlations were assessed with the full data and without the participant who had only ten interventional days. Correlations were calculated as parametric and non-parametric.

DTxP and Sham placebo arm EDA data were used in the analysis. For the analysis of DTxP arm, as with the movement data, the segmentation of the EDA data for action and no-action segments was used. Data before first action of the day were removed from the analysis to compare DTxP to no-action Sham data. Sham arm data were fully labelled as no-action data.

EDA signal is typically separated to “tonic” and “phasic” components (“tonic” as slow and “phasic” as faster signal variance) (Posada-Quintero & Chon, 2020). The analysis here was done for the “phasic” component. Removing tonic component makes the EDA signal more sensible to analyze (**Figure 9**). To remove the “tonic” component, the difference in two consecutive timepoints ($t2 - t1 = \Delta$) of the EDA signal was analyzed.

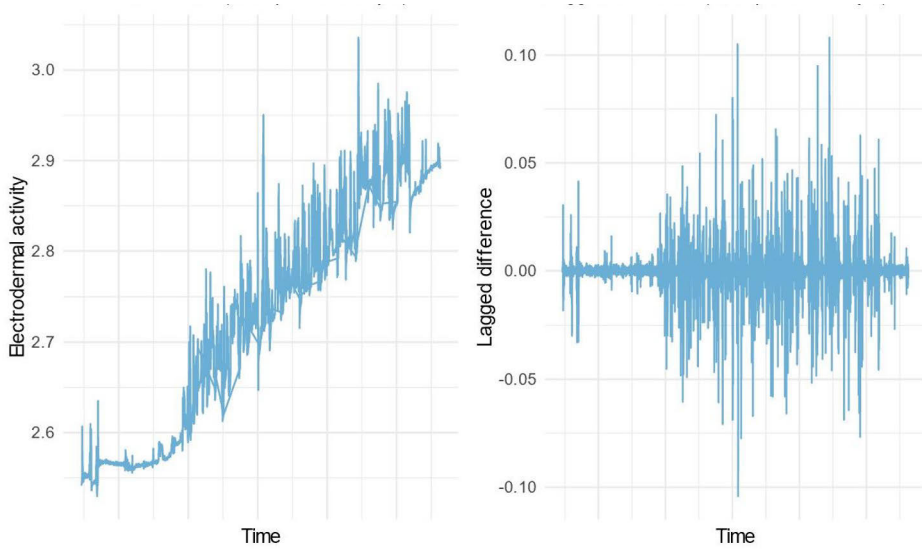

Figure 9. Example of EDA signal before (left) and after (right) removal of the "tonic" component

The peaks of Δ were counted and formed as *peaks/minute* value to measure "phasic" changes in the period. To distinct high peaks per minute, bands using median absolute deviation (MAD) were formed:

$$MAD = Median(|x_i - Median(x_{1..n})|)$$

MAD is a robust measure of variability, and it works better in outlier detection compared to standard deviation. Peaks were defined as Δ higher than median by 2-fold MAD. Peaks were normalized by counting ratio for average peaks per minute:

$$\frac{Peaks}{Minute} = \frac{count(\Delta x > 2 \cdot MAD(x))}{Segment\ Length\ in\ Minutes}$$

A visualization of the peaks and a peak band from a random EDA data is shown in **Figure 10**. Peak count per minute distributions were compared between different groups using a visual inspection.

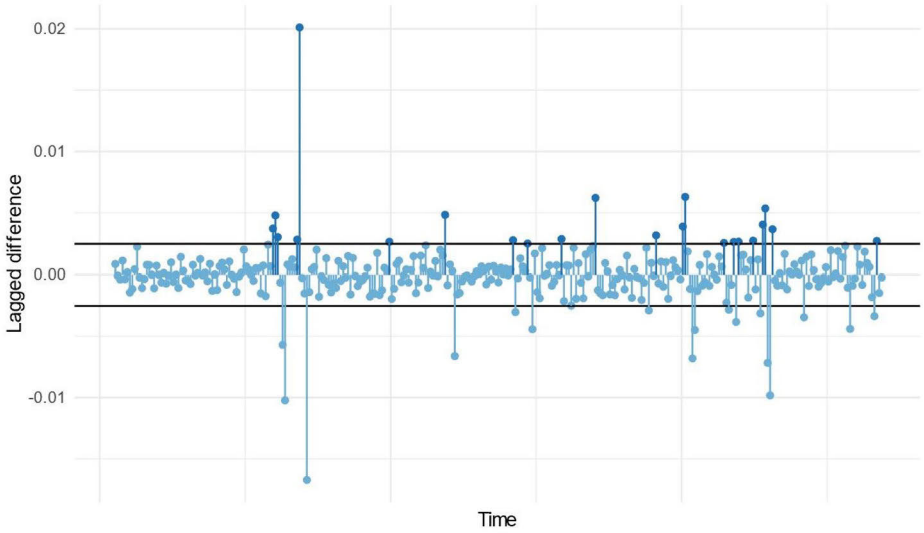

Figure 10. Example EDA peak bands and peaks

The general activity was analyzed by first visualizing the available aggregated data and its distributions between trial arms over time. Next, a regression coefficient model for the effects of group and day with each participant having an own regression line terms were assessed. Unfortunately, no detailed data (e.g., heart rate raw data) were available.

A variational autoencoder (VAE) was trained by using MJFF dataset (MJFFd) to identify the characteristics of a block of movement (movement state in PD) before the actual analysis of symptoms for that block was performed. Without finding these descriptors for the classification of different movement states, the analysis of the symptoms from the RWD was assessed to be too complicated, especially with the given population size. In other words, without understanding "*what kind of activity a person is doing*", it is difficult to try to detect motor symptoms (e.g., tremor) from the actual movements in the noisy and longitudinal accelerometer data.

Implementation of VAE was done by using PyTorch. The encoder was a two layer fully connected neural network with node count of 400 and 20 for the first and second layer, a symmetric decoder was used. From MJFFd a subset of right-handed patients who wore the accelerometer on their right hand was chosen. The VAE was trained using 10 second blocks of three channel accelerometer data.

A 20-dimensional latent representation of a given block of accelerometer data was used for a downstream classification task to different movement tasks. Classification was done by using a fully connected neural network with two hidden layers with 50 nodes each from the scikit-learn library. Classification accuracy was

determined by fivefold cross validation. Further validation was done by training the VAE model on patients from one test site and performing cross validated classification using patients from another test site.

From DAISY dataset demographic and baseline characteristics and efficacy and safety data were summarized by using descriptive statistics. No formal statistical hypotheses or sample size calculations were specified for this study.

Wearable and mobile-device data collected from participants with PD and without PD during the follow-up period were analyzed by using exploratory data analysis with R and Stan. Data from all available Garmin sensors, and subject's recordings of levodopa treatment intake and OFF period labels were used. The emphasis in data analysis was on tremor and bradykinesia. All reported symptoms with duration shorter than 2 hours were accepted, and the analysis was synchronized to the center of a symptom block (about 10-20 blocks of 21.8 minutes, 88% acceptance rate). Data with sampling problems was discarded. The data analysis included a pre-processing of acceleration signal channels with a high-pass filter (0.1Hz), an estimation of gravity with a low-pass filter, and a creation of virtual channels fixed to the estimated gravity and its temporal derivatives (XYZ channels and channels relative to estimated g, and PCA-like channels of principal oscillation for both channels).

Finally, a similar VAE as with the MJFFd was created by using the wearable data collected in our own study. The VAE was compiled using the same architecture, and the performance of this VAE was tested against the whole MJFF dataset.

4.6 Ethical issues

The VIRE study protocol and consent forms were reviewed and approved by the Ethics Committee of the HUS Hospital District, Finland (*HUS/1543/2019*). The VIRPI study protocol and consent forms were reviewed and approved by the Ethics Committee of the HUS Hospital District, Finland (*HUS/3111/2019*). The DAISY study protocol and consent forms were reviewed and approved by the Research Ethics Committee of the Pirkanmaa Hospital District, Finland (*R19051*).

All participants in these studies signed a written informed consent to participate in the study.

5 Results

5.1 Assessment of pain with CLBP (I-III)

5.1.1 Laboratory grade movement data analysis (I)

The visual inspection of laboratory grade movement data shows immediate differences between the healthy and CLBP participants. The examples of positional data trajectories of the first three movements with the left hand for both healthy user **Figure 11 A-B** and for the user with CP are visualized in **Figure 11 C-D**. Interestingly, even without applying any data analysis for the data, a clear difference can be observed between the users. The trajectory with the healthy individual (A and B) seems to be a lot smoother than for the user with CP (C and D). The observed difference is supporting the intuitive hypothesis of chronic pain patients having less smooth movements than health participants, and also means that the differences in movement data should be explored further.

The more accurate visual analysis of movement data by plotting the data by coordination axes, from the left hand from all eight patterns of movements are visualized in **Figure 12** (healthy individual) and **Figure 13** (participant with CLBP). The difference in movement data visualization when the hand is active and when the hand is not active is clear.

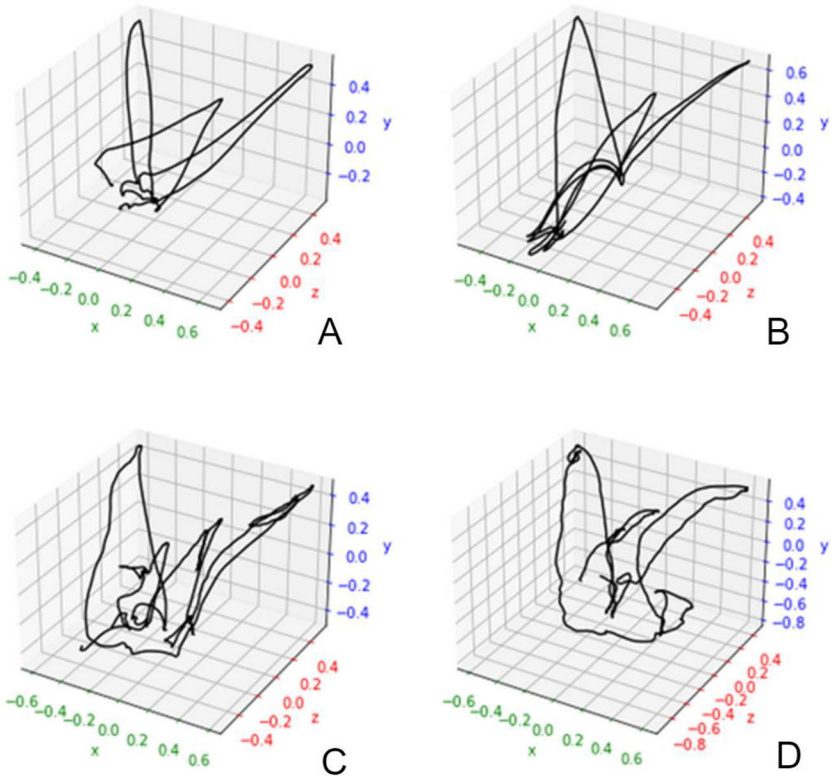

Figure 11. The first pattern of movements with the left hand. The trajectory of the hand is plotted in a 3-dimensional space. A and B are trajectories from healthy individuals, C and D are from patients. Visually it can be seen that the healthy individuals seem to have a smoother pattern (above) than the patients (below).

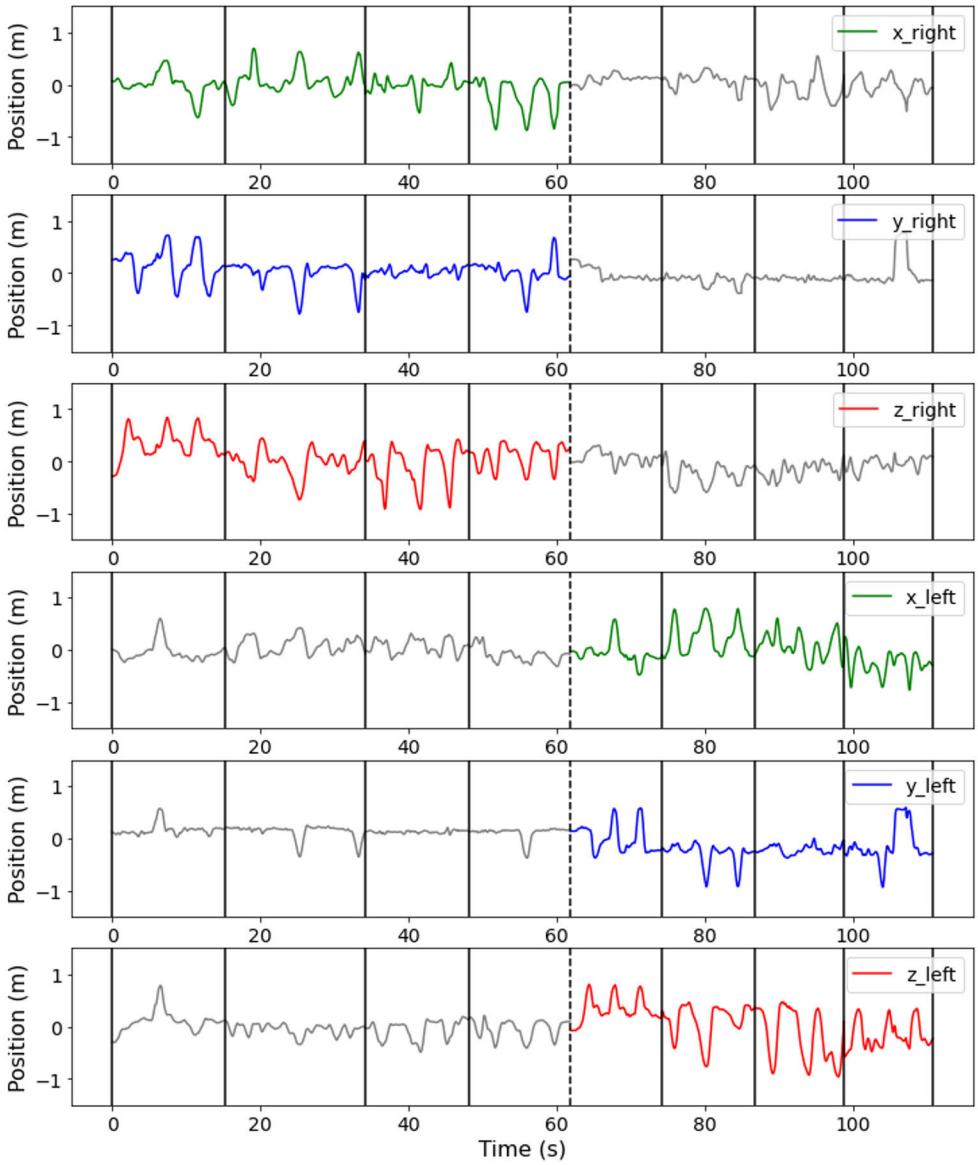

Figure 12. An example of the movement data from a healthy individual. First four patterns of movements are done with the right hand and the next four with the left hand. The active hand is marked with colors. X-axis is movements from left to right, y-axis is vertical movements, and z-axis is movements from front to back. The first four patterns seemed slower than the last four, as the subject learned the patterns. No clear pattern in the data of the passive hand is seen.

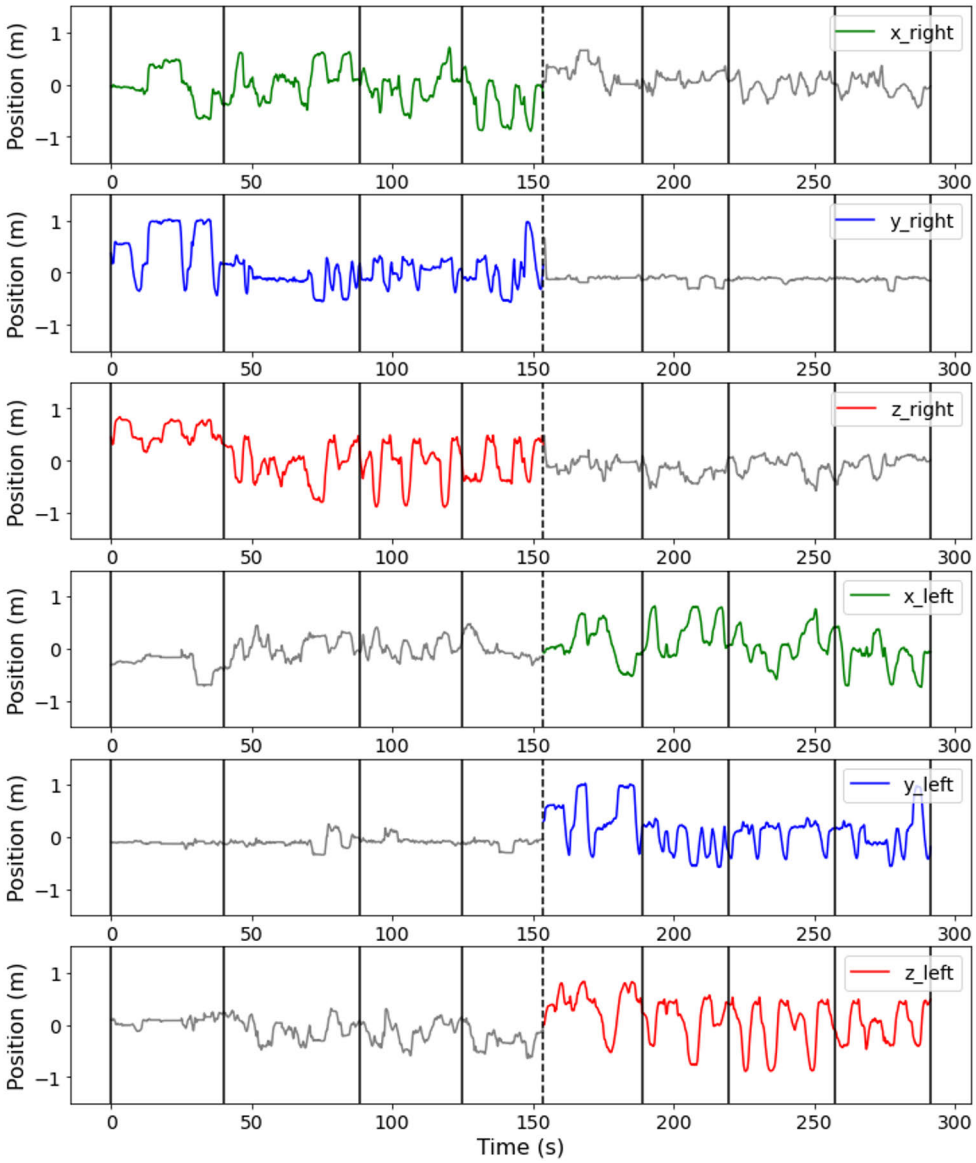

Figure 13. An example of the movement from a CLBP participant. First four patterns are done with the right hand and next four with the left hand. The data of the active hand looks like **Figure 12**. Note the different scale of the x-axis between these figures. The participant with CLBP performs the movements slower than the healthy participant.

Next the movement data features were further explored and analyzed. **Figure 14** shows the selected features for the first pattern of movement with the left-hand. The time spent on the pattern, and the variance of velocity when doing movements can separate the patients and controls well. Accordingly, the p-values for these in all patterns in the left-hand data in the two-sample t-test are below 0.05 (**Table 4**). However, the mean and variance of the distance between the head and the active hand do not discriminate the two groups well. Also, p-values for these are above 0.05 in all patterns.

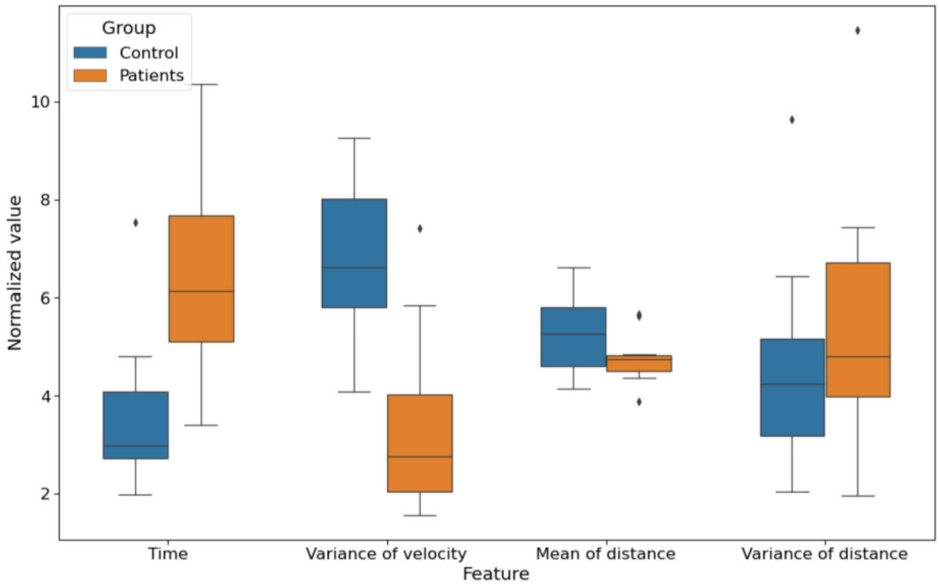

Figure 14. Example of different features in the first pattern with the left-hand tasks between the patients and the control participants. Time and variance of velocity have non-overlapping distributions between the groups. However, the mean of distance and the variance of distance have overlapping distributions.

Table 4. P-values in the Two-Sample t-Test for the features in the movement data patterns with the left-hand data.

	TIME	VARIANCE OF VELOCITY	MEAN OF DISTANCE	VARIANCE OF DISTANCE
Pattern 1	0.0035	0.00096	0.16	0.52
Pattern 2	0.001	0.000003	0.29	0.98
Pattern 3	0.000117	0.000006	0.063	0.86
Pattern 4	0.000009	0.000005	0.051	0.21

Next, the performance of different HMM methods were explored. The objective was trying to understand how different HMMs can segment time series data, and what HMM was the best in the segmentation. The same pattern of movements from a user with CP and from a healthy user, by using positional data, velocity calculations, and normalized velocity calculations in segmentation are shown in **Figure 15** and **Figure 16**. Only z axis data is shown, however the models were fitted with full 3D data.

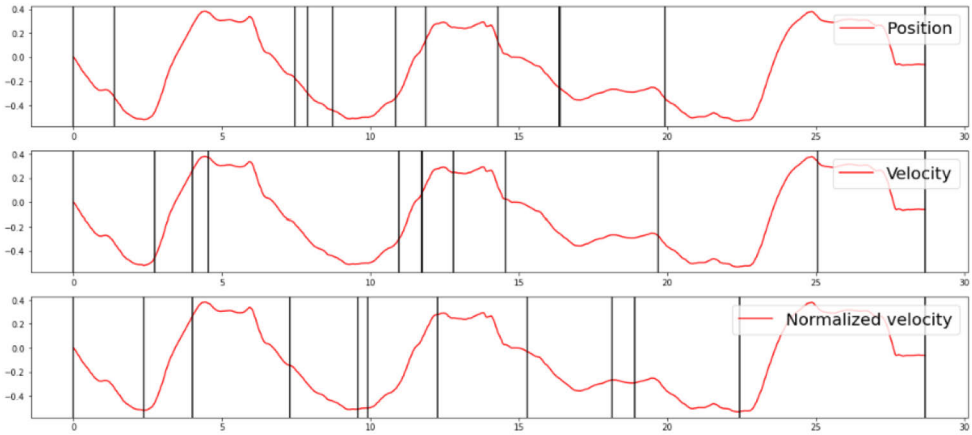

Figure 15. Segmentation of a pattern of movements (only z axis “red line” data shown) from a patient, using positional data, velocity, and normalized velocity. Vertical lines show the segmentation by HMM.

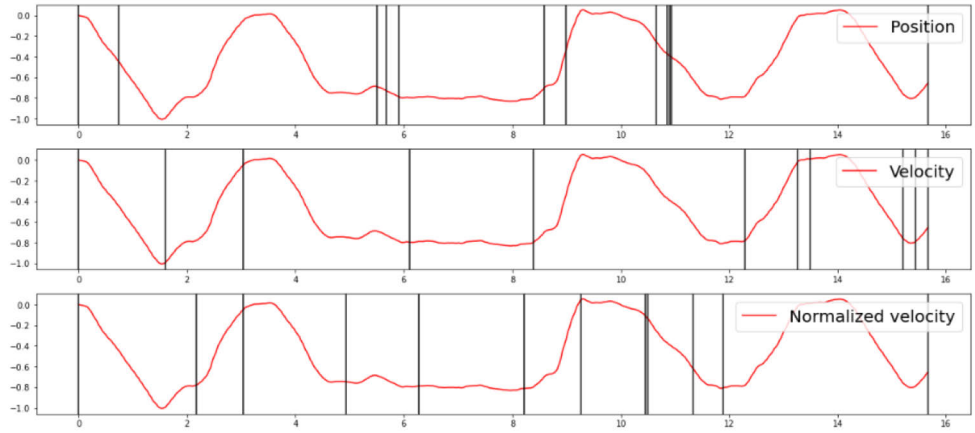

Figure 16. Segmentation of a pattern of movements (only z axis shown) from a healthy control, using positional data, velocity, and normalized velocity. Vertical lines show the segmentation by HMM.

HMM by using positional data ("Position") misses essential information. The model does not segment the first and last peak. HMM with "velocity" segments the second red peak in multiple parts, but completely leaves the peak unsegmented in this figure. HMM with the "normalized velocity" is the only model that segments the time series of these two subjects consistently. The similar performance was observed when plotting other time series than the ones shown as these examples.

Figure 17 and **Figure 18** visualizes the segmentation of a healthy user and a user with CP movement data with HMM that uses "normalized velocity" data from all dimensional channels. This HMM model was able to do so consistently regardless of the cohort or the time spent when doing the movements in the pattern.

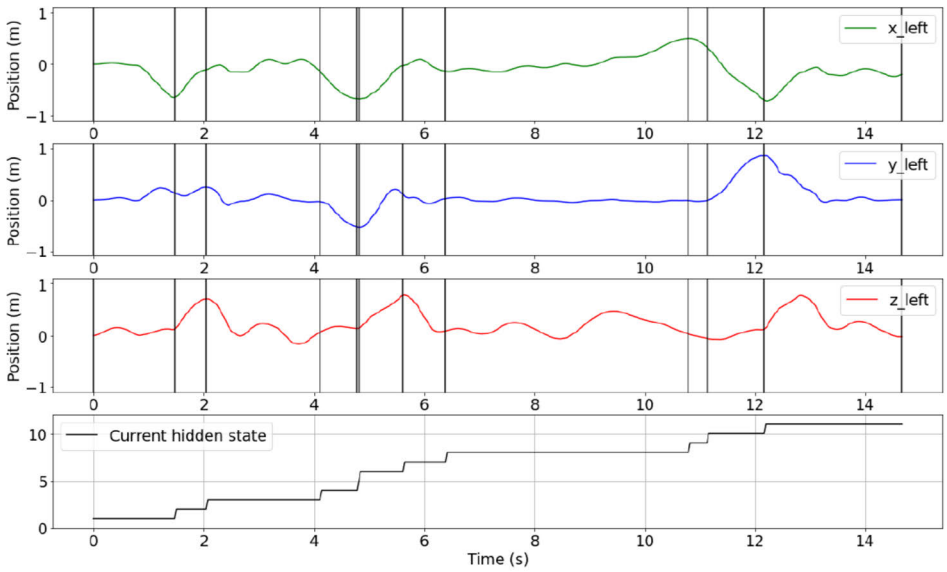

Figure 17. Segmentation the last pattern of movements of a healthy participant by using a HMM with normalized velocity data

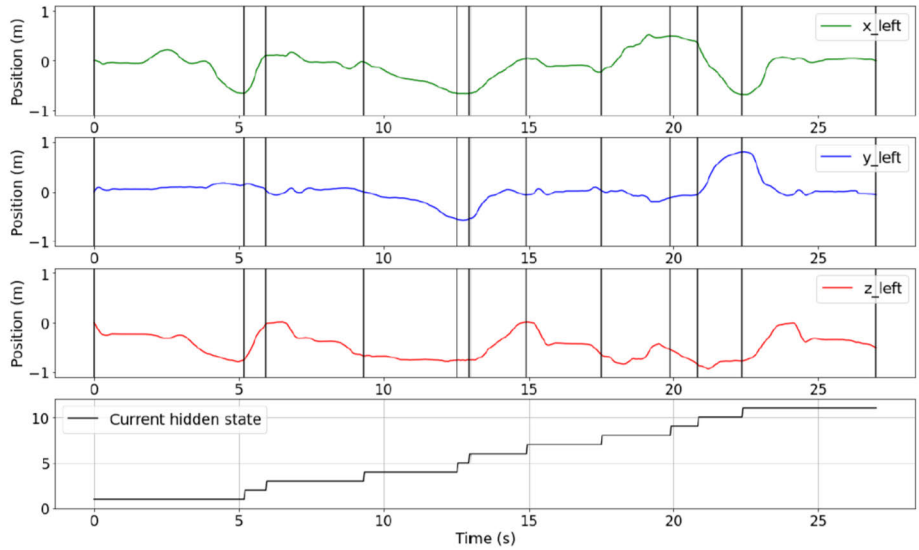

Figure 18. Segmentation the last pattern of movements of a participant with CP by using a HMM with normalized velocity data.

A posterior predictive checking with simulated data shows that the data generated with a “normalized velocity” HMM were similar to the actual laboratory grade data (**Figure 19**). With the major movements, like moving a hand to a dimension, real world and generated data looked very similar, though the RWD had less edgy shapes than the generated data.

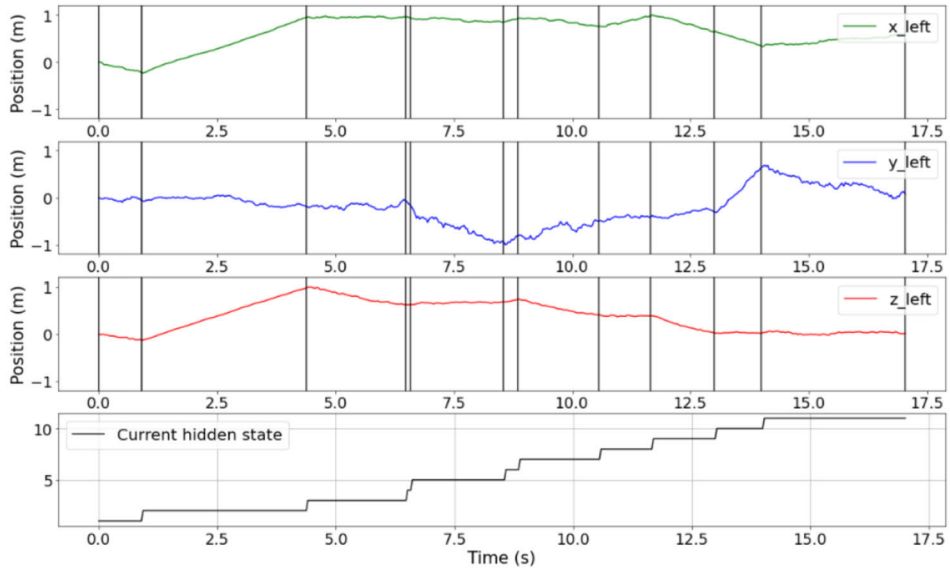

Figure 19. Posterior predictive checking with a HMM that uses normalized velocity.

5.1.2 RWD analysis correlates with clinical outcomes (II, III)

The analyzes of the RWD in CLBP begins with the VIRPI study clinical results. The study reported statistically significant benefit over comparison interventions for fear of movement (**Figure 20**), patient clinical global impression of change (PGIC) and quality of life (Eccleston et al., 2022).

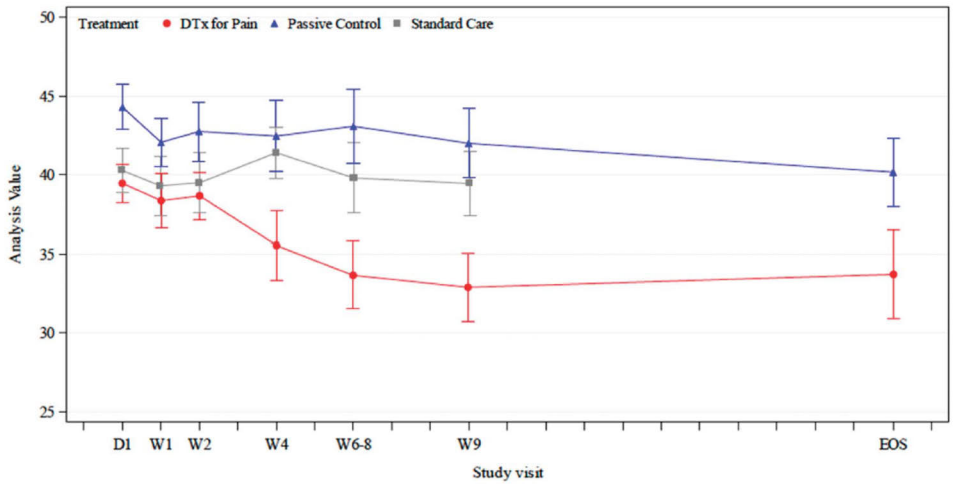

Figure 20. Tampa Scale of Kinesiophobia scores between groups in VIRPI study.

As with the laboratory grade wearable data the analysis of the wearable data begins by segmenting the data. The segmentation here was manual, by action vs. no-action segmentation, where the action meant the data when the user was doing the exercises in the VR treatment. Different no-action segments, and the average velocity of sensors in all segments are shown in **Figure 21**. The action data has higher velocity on average. This supports the used segmentation logic and is also in line with the findings in the laboratory grade wearable dataset. As the participants were first preparing for activities and at the end of day, they stop activities while movement is still recorded. The no-action segments between actions are closer to action segments in distribution of velocity, as the participants were more engaged in VR environment.

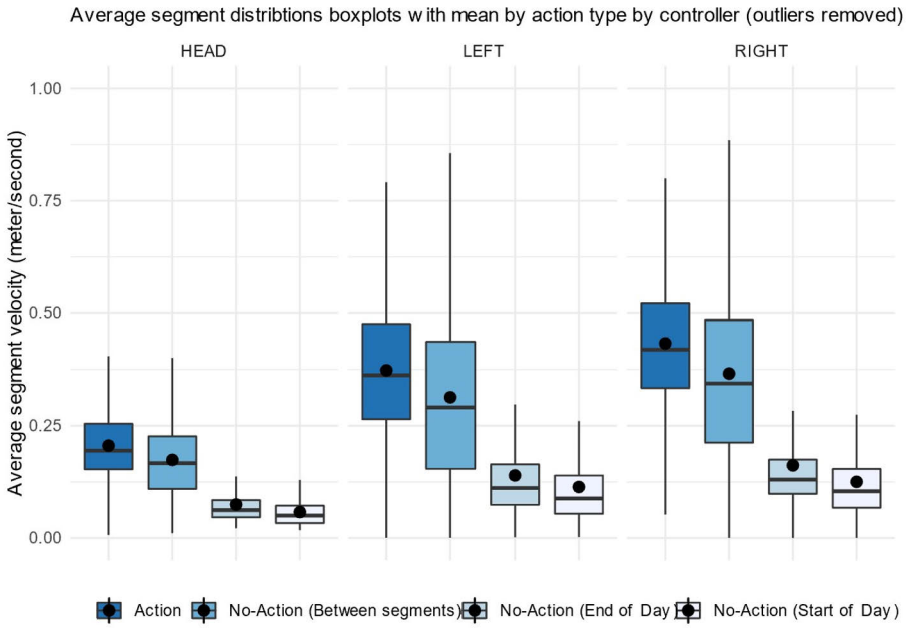

Figure 21. Average velocity (m/s) in movement segments in different accelerometer sensors (head mounted VR device, left-hand and right-hand controllers) by action type.

Next the action segments alone were used to assess the average velocity. Velocity over time was explored by fitting a regression line to the average velocity of action task segments during the study days. The velocity of the right-hand for every participant is shown as an example in **Figure 22**. The results for the left-hand and head controllers look very similar.

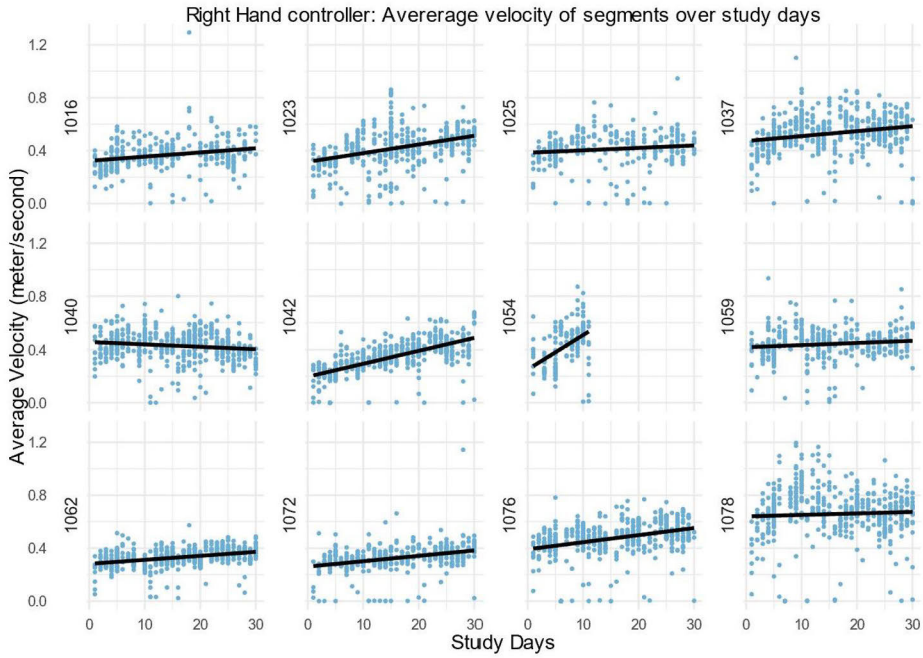

Figure 22. Average velocity in the right-hand controller of all action task segments within the 30 daily sessions (m/s) for all DTxP arm participants, with the regression line over the time.

The velocity seems to increase for almost all over the study. This was also one of the key objectives with the treatment. A similar trend can be seen in left-hand and head controller movement data.

The slope of the regression line for the participant 1054 is three folds more than any other slope. One can see by looking the regression lines that the first study days seem to have more slope than rest of the days. This could likely cause bias when including 1054 without the remaining days with as limited population as here.

Correlations between the slope of average velocity values in the controllers and the change in TSK, Overall health VAS and EQ5D5L QoL scores during the study were calculated (**Table 5**). Controller values are estimated as the slope of daily change multiplied by study days. Participants had 29-30 study days in VR, except participant 1054 who had only 11.

Table 5. Average change of velocity as "**slope value * study days**" (m/s) in right, left and head controllers, and the change in clinical assessments (Tampa Scale of Kinesiophobia (TAMP), Overall health Visual analogue scale (VAS), EuroQoL-5D-5L QoL score (EQ5D) during the study for each participant in DTxP arm.

SUBJECT	TAMPA	VAS	EQ5D	HEAD	LEFT	RIGHT
1016	-6	20	-4	0.054	0.077	0.095
1023	-6	53	-4	0.111	0.181	0.197
1025	7	-5	4	0.046	0.127	0.055
1037	-12	50	-4	0.066	0.067	0.113
1040	-2	5	0	-0.017	-0.055	-0.055
1042	-8	15	-1	0.088	0.185	0.283
1054	-4	-20	2	0.174	0.200	0.287
1059	-8	15	-3	0.069	0.253	0.049
1062	-11	60	-4	0.070	0.163	0.090
1072	-9	25	0	0.059	0.162	0.122
1076	-8	40	-6	0.074	0.158	0.182
1078	-7	-15	1	0.046	0.027	0.011

The Pearson and Spearman correlations of the head, left-hand and right-hand controller velocity values, and the clinical endpoints without and with participant 1054 are shown in **Table 6** and **Table 7**.

Table 6. Pearson correlations of the average velocity slopes in the movement controllers and the clinical endpoints in DTxP arm **without participant 1054 / full data** during the study.

	TAMPA	VAS	EQ5D	HEAD	LEFT	RIGHT
TAMPA	*					
VAS	-0.59 / -0.58	*				
EQ5D	0.71 / 0.70	-0.78 / -0.82	*			
HEAD	-0.40 /-0.17	0.55 / -0.02	-0.47 / -0.02	*		
LEFT	-0.23 / -0.18	0.37 / 0.18	-0.29 / -0.16	0.79 / 0.71	*	
RIGHT	-0.34 / -0.22	0.47 / 0.11	-0.40 / -0.13	0.83 / 0.86	0.61 / 0.64	*

Table 7. Spearman correlations of the average velocity slopes in the movement controllers and the clinical endpoints in DTxP arm **without participant 1054 / full data** during the study.

	TAMPA	VAS	EQ5D	HEAD	LEFT	RIGHT
TAMPA	*					
VAS	-0.59 / -0.65	*				
EQ5D	0.43 / 0.55	-0.81 / -0.84	*			
HEAD	-0.45 / -0.24	0.67 / 0.29	-0.66 / -0.33	*		
LEFT	-0.29 / -0.15	0.36 / 0.08	-0.25 / -0.04	0.76 / 0.80	*	
RIGHT	-0.33 / -0.16	0.56 / 0.20	-0.50 / -0.20	0.79 / 0.85	0.52 / 0.57	*

Both the velocity slopes and the clinical scores are strongly correlated within their respective groups. The increased activity means the increased movement velocity in all sensors, and the obviously the clinical assessments are all validated questionnaires. The correlations between velocity slopes and clinical assessments are on a moderate level. For TSK and EQ5D the increasing velocity slope correlates with a negative change. With VAS change the correlation is positive. The increased velocity thus shows promising correlation with the improving clinical assessments.

There was not enough EDA data to find statistically meaningful results. However, the peaks/minute -measurements between DTxP and Sham arms by study day were still promising. Overall, there were more peaks/minute in early study and some higher distributions in DTxP arm by the end of study. However, the association was not clear. In comparing peaks/minute -measurement distribution by participant, the distributions were organized by median (**Figure 23**).

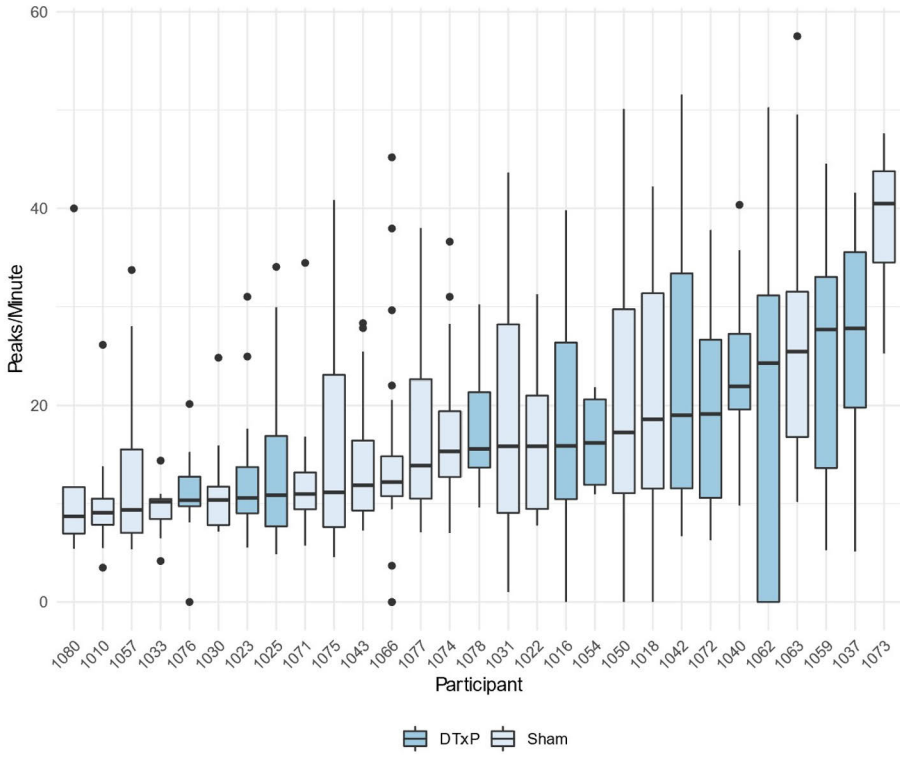

Figure 23. Number of electrodermal activity (EDA) peaks per minute by participant, organized in the ascending order by the median.

DTxP arm seems to have a higher median with larger variability. Sham arm had more participants with clearly narrow distribution with a low median.

When it comes to general activity data, the heart rate, steps, and sleep duration aggregates from the wearable device were collected. The population size to analyze daily averages was too low, though the steps were still somewhat promising. The change in daily mean was calculated and aggregated to weekly measure. Then change distribution over all patients was plotted and analyzed (**Figure 24**). Some difference in the change in daily steps can be seen between the groups.

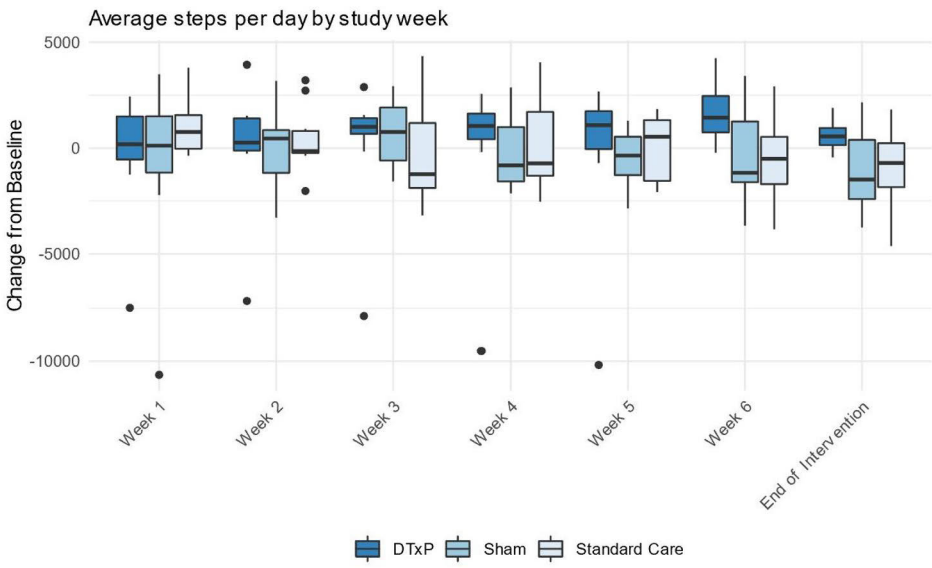

Figure 24. Average steps per day by study week.

5.2 Assessment of symptoms in PD patients (IV)

5.2.1 VAE detects movement states in MJFFd (IV)

Effect of the drug state on symptoms can be seen in both accelerometer and observer scores, and with expected polarity, which means dyskinesia is amplified, and bradykinesia and tremor attenuated by the levodopa treatment. The effects on bradykinetic accelerometer scores are shown in the **Figure 25**.

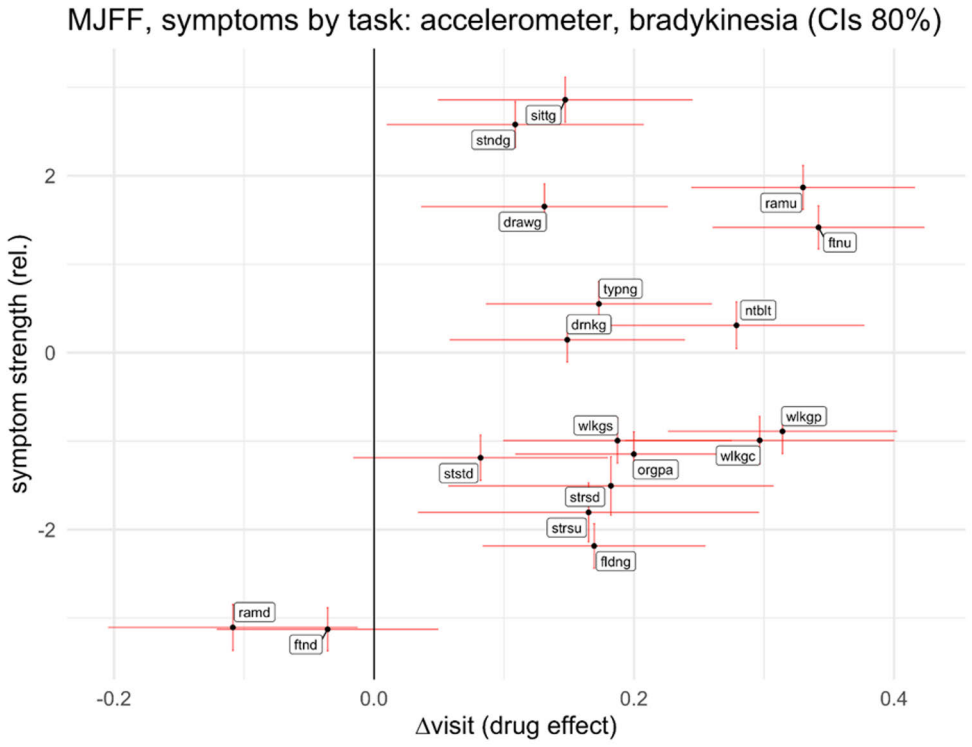

Figure 25. Drug effect on the bradykinetic symptom severity as predicted from the accelerometer data (x-axis), and relative strength of the effect (y-axis) at different tasks in MJFFd.

In the figure, task types are depicted by acronyms (full list can be found from **Table 2**). X-axis shows the difference from the drug state, and the y-axis the strength of the symptom signal as seen by the linear spectral model. Of these, the effect of levodopa (x) is more meaningful, because it shows the effect of a well-controlled manipulation in a constant movement state. We see clear differences across tasks; especially ramu (repeated arm movement, undominant hand) and ftnu (finger to nose, undominant) are discriminative, also wlkgp (walking through a narrow

passage), wlkgc (walking while counting) and ntblt (assembling nuts and bolts). Other symptom types show larger uncertainty in drug effects (figures in the Appendix), but notably, ramu and ftnu again show good discriminative ability for dyskinesias. Scales on the axes are commensurable but otherwise artificial.

A similar analysis for the observer scores was performed. Bradykinetic scores are shown in **Figure 26**.

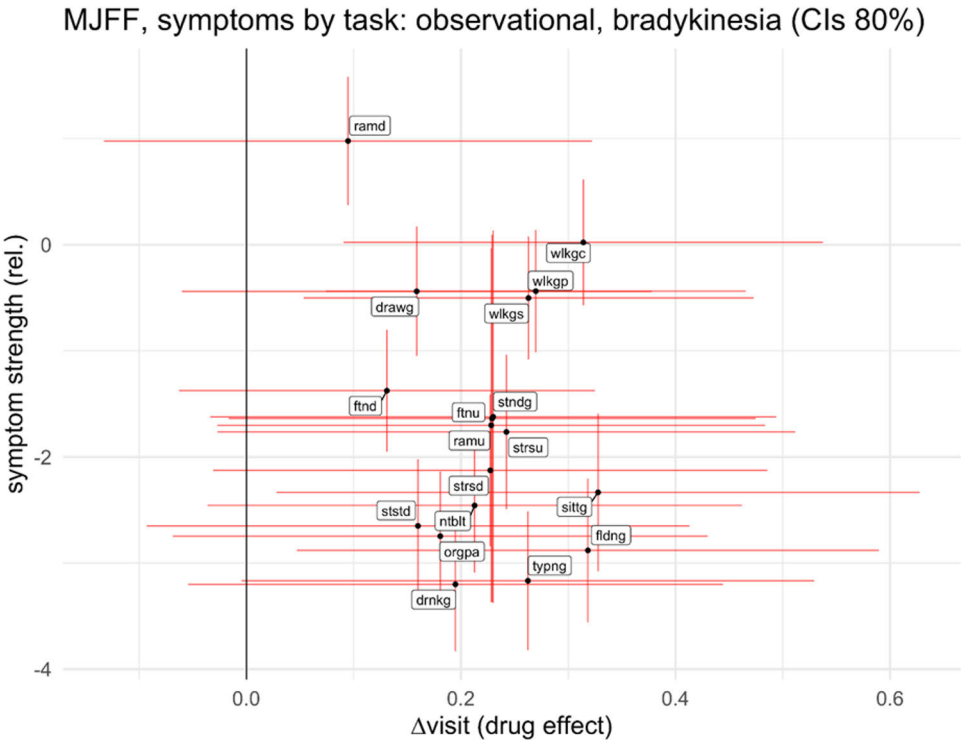

Figure 26. Drug effect on the bradykinetic symptom severity as seen by the observers (x-axis), and relative strength of the effect (y-axis) at different tasks in MJFFd.

Modelling uncertainty here is higher, indicating more noise in observer scores compared to the accelerometer. Partly due to noise, it is hard to say whether symptom visibility across tasks is like that with the accelerometer, but the discrepancies would not be unexpected, because obviously visual vs. kinetic observability may vary across situations.

In conclusion, these results suggest that even simple linear models can see symptom signals from the accelerometer data, and that their capability is modulated by the task, or movement state, of the subject. The dyskinetic accelerometer scores

are amplified, whereas tremor and bradykinetic scores are attenuated by the levodopa treatment.

Next a VAE for movement types was implemented. The validation was done by training the VAE model on patients from Boston test site and performing cross validated classification using patients from New York test site. As a second test, we trained the VAE using our own patient accelerometer data and performed the prediction task on the MJFFd population.

When training the VAE model on MJFFd, a mean classification accuracy of 0.48 for the eighteen different tasks was obtained. Random guessing would give a rough baseline accuracy of approximately 1/18 (~6%). A notable feature of the confusion matrix (**Figure 27**) is the grouping of confusion among similar tasks: the upper left corner indicates confusion among walking tasks, and the lower right corner shows confusion among fine motor tasks. Since some of the tasks are performed unilaterally, we can also see confusion among tasks where the non-performing hand is approximately stationary: sitting, finger to nose left, and repeated arm movement left.

The predictor differentiated the tasks well above random guessing without any tuning, implying the VAE learned meaningful movement-state representations.

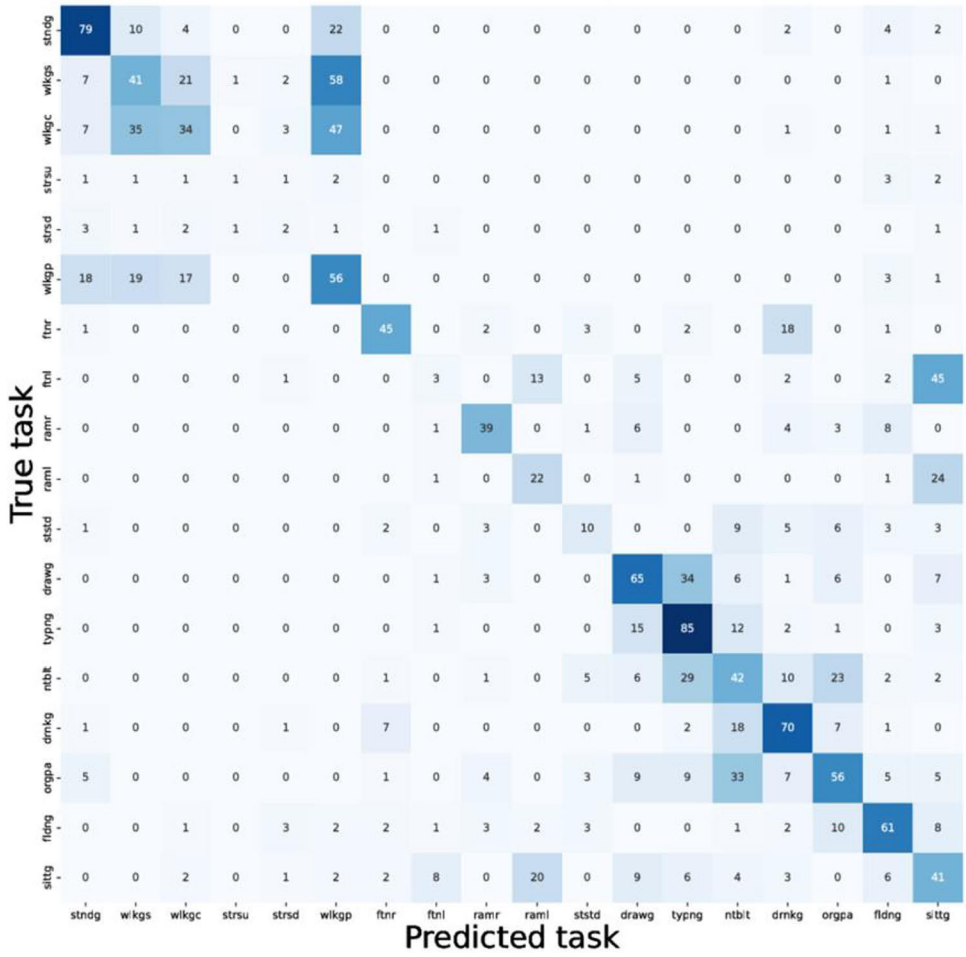

Figure 27. A confusion matrix for predictions of tasks using representations from a VAE trained on MJFF data. Data from Boston site was used for training, and data from NYC site for testing (see **Table 2** for abbreviations)

5.2.2 Spectral analysis of accelerometer data (IV)

Analysis of all spectral data shows partial separability of patients and controls. **Figure 28** shows spectral differences between patients and controls as z-scores; z-scores are for block means of dB-scale spectra over all data (and therefore ignore annotations, and patients as a replication unit). Z-score is calculated as $\frac{(mean\_P - mean\_C)}{\sqrt{\left(\frac{var\_P}{n\_P}\right)+\frac{var\_C}{n\_C}}}$, where mean are means of log-amplitudes over the 21.8-minute blocks at the target frequency, for patients and controls, var are variances, and n are numbers of blocks.

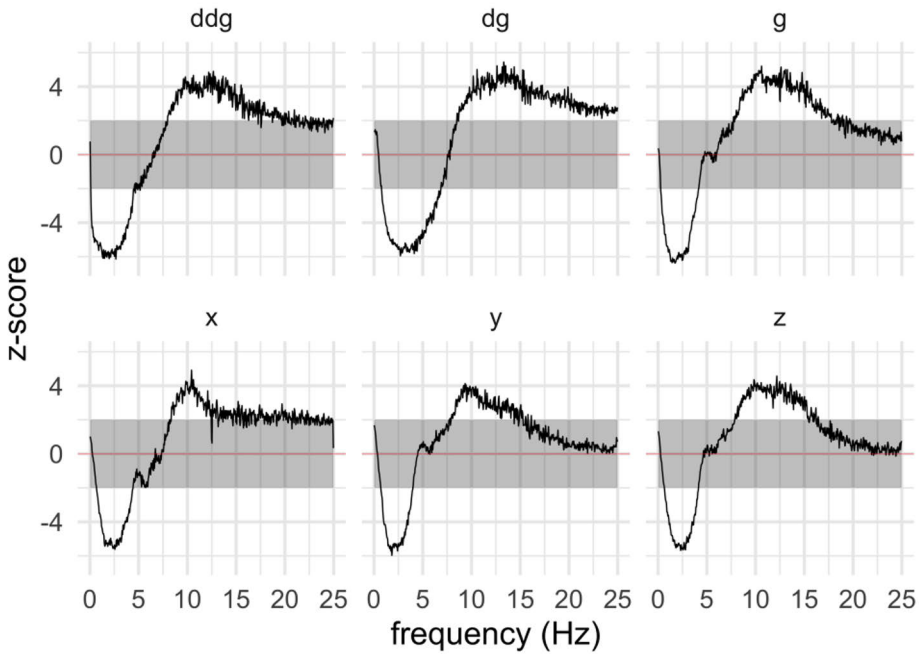

Figure 28. Temporally aggregated power spectra of device and g-aligned channels patients vs. controls

Separating patients from controls based on the x-channel spectrum only gives leave-one-out ROC (**Figure 29**).

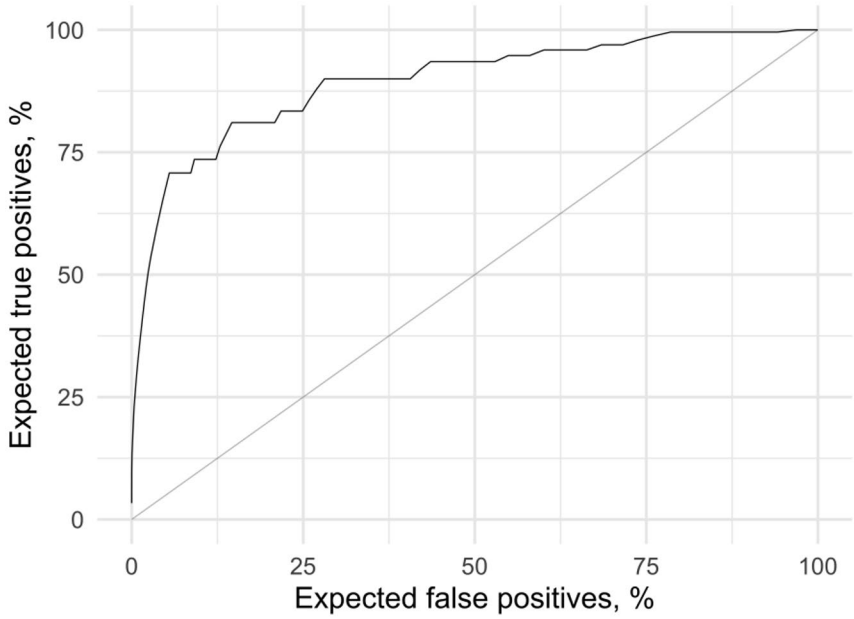

Figure 29. leave-one-out ROC curve (AUC = 0.895)

Using all available pre-processed wearable data, a promising (AUC = 0.895) classification is gained.

Characterization of symptom events of patients with spectral, temporal, and across-channel envelopes are shown in **Figure 30**. The top row is for tremor, the bottom row for the rest. The tremor events have a spectral spike at around 5 Hz, and attenuation at lower frequencies, while other symptoms show attenuation at low frequencies. Tremors are temporally more focused around the reported time. Channel responses show varying visibility, with the physical ones (x, y, z) being similar to the derived virtual channels (g, dg, etc.). Tremor is less visible on the x-channel because that channel is parallel to the limb.

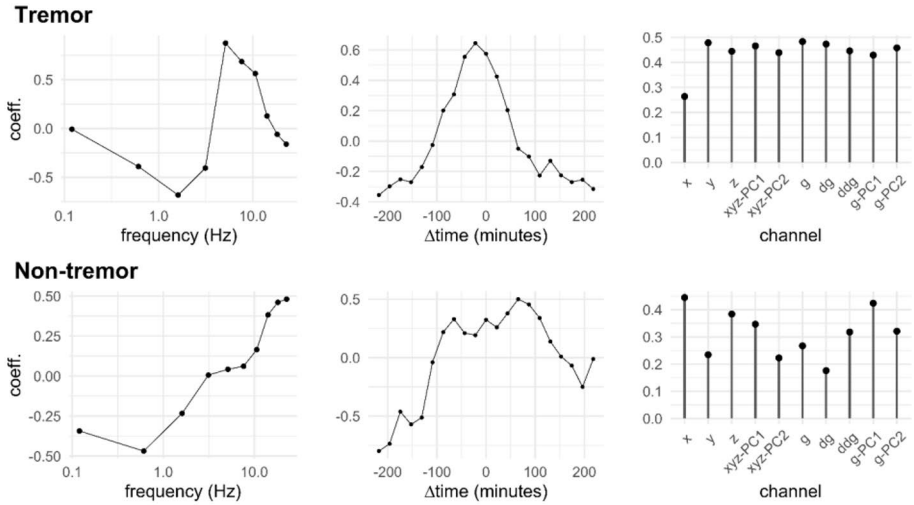

Figure 30. Spectral, temporal, and across-channel envelopes of tremor symptom data (top) and rest of the symptoms data (bottom)

As a summary, the linear models on spectral features do see the signal.

Finally, when the VAE model (like the one developed in with MJFFd) was trained with the real-world accelerometer data and tested on MJFF data a mean classification accuracy of 0.41 was achieved. Again, a lot higher than just random guessing (= 1/18 ~ 6%).

5.3 Usability of RWD collection methods (II, IV)

In CLBP, the VIRPI study reported a high usability for the DTxP arm measured by using the modified Game experience Questionnaire. The assessments at end of the intervention (weeks 6-8) compared to the Sham placebo comparator are much better as can be seen in **Figure 31**. Also, the change from the beginning of the study to the end of the study is much less. The small change can be of course explained by the fact that DTxP was designed to be a treatment, not a data collection method.

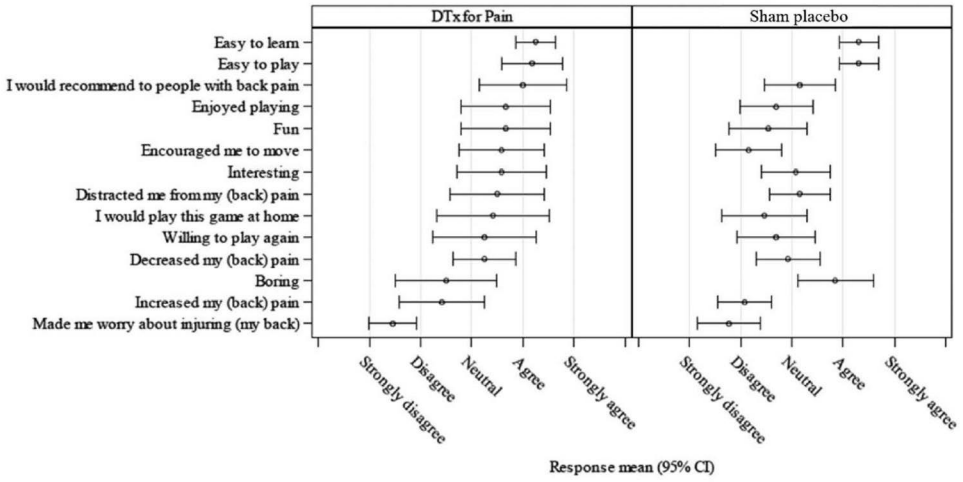

Figure 31. Modified Game experience Questionnaire at End of Intervention visit (6-8 weeks)

In PD, 63/65 subjects responded to the usability questions, however some did not answer to all questions. Usability assessments can be seen from **Table 8.** Usability of wearables and mobile application, and despite there are things (e.g., charging of devices and recording bad moment during the symptom) to improve, the overall usability made the execution of study conduct in real life possible.

Table 8. Usability of wearables and mobile application

	PD patient (n = 36)	**DBS PD patient (n = 6)**	**Control (n=23)**
Question	**n (%)**	**n (%)**	**n (%)**
Wearing device entire day: very easy or easy	32/36 (88.9%)	4/5 (80.0%)	21/22 (95.5%)
Charging device and phone: somewhat or very difficult	13/36 (36.1%)	2/5 (40.0%)	7/22 (31.8%)
Levodopa reminders helpful?	26/35 (74.3%)	3/4 (75.0%)	-
Recording bad moment now: very easy or easy	25/36 (69.4%)	4/5 (80.0%)	-
Recording previous bad moment: very easy or easy	24/36 (66.7%)	4/5 (80.0%)	-
Learned more of condition with the app?	29/36 (80.6%)	0/5 (0.0%)	-

6 Discussion

The research of novel digital diagnostic methods and biomarkers in CP is not very advanced yet. The symptoms in CP are personal, subjective and a context dependant experience, and thus the attempts to find suitable wearable signals systematically and reliably reporting the experience pain has been found challenging. Heart rate variability is one of the most promising measurements, but the evidence is still very limited, and further research on understanding the HRV varies in a smaller time frame (e.g., minutes, hours) instead of days or weeks, is needed (Bandeira et al., 2021). Furthermore, HRV seems to be more powerful in the detection of ND symptoms in situations where "multi-modal sensor data" is available instead of just HRV data alone (Spasojevic et al., 2021). Measuring EDA is a more difficult method, as the signal value is not only dependant on the person's physiological skin reaction but is also dependant on the surrounding temperature and humidity (Posada-Quintero & Chon, 2020). The research on surrogate measurements of CP such as overall activity and sleep has been more successful (Fjeld et al., 2022; Hisamatsu et al., 2022; Zambelli et al., 2022). This also matches with the findings in this thesis, as the movement data was found to be more promising surrogate signal in CLBP compared to EDA, general activity, and average of daily heart rate. There have been some studies done over general movement data in CP (Hisamatsu et al., 2022; Tsang et al., 2022; Xu et al., 2021) with promising results of improved overall activity correlating with improved clinical outcomes. However, when trying to analyse the accurate movement data, again with the improving scores correlating with the better clinical assessments, the measurement arrangements have so far been rather laborious, e.g., using 3D imaging devices in the detection of movement instead of accelerometer sensors (Papi et al., 2020; Zambelli et al., 2022).

In this thesis laboratory-grade movement data was collected and analysed to identify features that could differentiate between patients with chronic low back pain (CLBP) and healthy controls. It was found that logistic regression models using both segmented and non-segmented data were able to classify patients and controls with similar and high accuracies (0.86). The time spent on movement tasks and the total variation of movement velocity were found to be promising features for differentiating between patients and controls. However, other features like

movement acceleration analysis and various cognitive tests while moving may also be useful in classification. The selection of features is more limited by the chosen data collection method and e.g., the context of the treatment. As an example, it would be interesting to request people to follow specific virtual object with their hand, and then measure the distance between the active hand and the object. To be able to apply this efficiently in the future, any individual task in the solution should be accurately annotated. This note, including carefully implemented use of timestamps, is vital for the future data analysis. That would also enable exploiting the range-of-movement research already done by other devices (Papi et al., 2020).

HMM was an interesting statistical model in which the system is assumed to be a process with unobservable ("hidden") states (Fink, 2014; Zhou et al., 2022). It has been used in different kind of time-series related pattern detection tasks such as with the eye movement analysis (Chuk et al., 2020; Chuk et al., 2017; Liu et al., 2021). It was assumed to be particularly well-suited for this analysis for several reasons. First, HMM is a flexible and powerful statistical model that can handle complex and noisy data. Movement data from accelerometers can be noisy and difficult to interpret, but the HMM is able to account for this noise and extract meaningful information from the data. Second, the HMM is a probabilistic model that allows for the incorporation of uncertainty and variability in the data. This is important in the analysis of CLBP movement data, as there can be a great deal of variability between individuals and even within the same individual over time. The HMM can account for this variability and provide more accurate and reliable results. Third, the HMM is a model that is well-suited for analysing sequential data, such as the time series data generated by accelerometers. The HMM can model the transitions between different states, allowing for the identification of patterns and trends in the movement data. This is particularly useful in the analysis of CLBP movement data, as it can help to identify changes in movement patterns that may be indicative of changes in the underlying condition. Furthermore, HMM can handle similar patterns in time-series even if the duration differs. HMM using normalized movement velocity data was found to be able to segment the data in a promising manner. This opens possibilities for defining even more detailed features, with a potential to improve the segmentation accuracy, when larger datasets become available in the future. The segmented data contains all the same information of the pattern that the non-segmented data, but also the *hidden* information structural information. Therefore, the segmented data has a lot of potential to improve the classification accuracy in the future. The logistic regression with segmented features outperformed the logistic regression with non-segmented features already with our small data set when the performance was measured in terms of average predictive likelihood. Furthermore, many machine learning algorithms with big datasets could find interesting and hidden relationships between segmented features, beyond the ability of logistic regression models. Some research on

exploiting HMM in the analyses of accelerometer data has been published, e.g., in osteoarthritis, however the analysis has again been more less accurate compared to this research (Xu et al., 2021).

This thesis exploited the collected clinical data and the sensor data from Oculus Quest, Empatica Embrace2 and Garmin Vivosmart4 sensor data from 39 participants in a clinical trial of a digital therapeutic for CLBP. With the accelerometer data the DTxP arm only was analysed. With the EDA data, the data between the DTxP and Sham placebo arms were compared. With general activity data, the data between all study arms were assessed. First it was explored how large and volatile datasets can be collected and analysed together with the clinical information. Then it was studied whether any specific data signals could be associated with clinical changes in outcome due to the intervention. The association between digital signals and clinical variables by using Pearson and Spearman correlations was assessed. Pearson is sensitive to outliers, whereas Spearman has less statistical power as it is using ranks, as shown in e.g., psychological research (de Winter et al., 2016). Both were used here because of limited sample size.

Not all data were useful. Despite useful learnings in the analysis of EDA, the noisy characteristics of data between the sessions made it not very useful with as limited study population. To put it simply: much more data is needed. EDA has though been already shown to be a very promising method in CP, especially in combination with other sensor data, such as accelerometer signal (Bonnet & Naveteur, 2006; Kong et al., 2022). Heart rate data were aggregated over a daytime and so lacking in precision for any meaningful clinical analysis. Again, heart rate, and especially its variability has been found a promising signal for chronic pain (Bandeira et al., 2021; Rausa et al., 2022; Yetwin et al., 2022). However, fine movement data of head and both hands were found to be more robust for further research and development. As discussed previously, combining various sensor measurements into one model might be the best approach in the future.

As also found with the laboratory grade data, the velocity of individual movements over time was selected as a target variable. In part because it was possible to segment the data over time and for its relevance to clinical outcomes. No segmentation of this data by using HMM with normalized velocity was tried. In the future this would be an interesting approach but requires well-thought and implemented collection and annotation of data. It was also found that for most of the participants the average velocity of all the sensors increased during these segments over the study. As the clinical study results and treatment objective also suggest, the fear of movement participant's movement improved over time. This longitudinal change correlated with the improvement in clinical endpoint measurements. The largest correlation with clinical endpoints was observed with head and right-hand sensors. The latter makes sense since participants were mainly right-handed, and the

increase in the movement is likely explained by them using intuitively the dominant hand in activities. What was very surprising is the even stronger correlation with the head sensor movement data and clinical endpoints. Yet it is too early to say that any body part sensor would not be a potential source for a digital movement biomarker in CLBP. More research is needed but it might be possible that CLBP patients with kinesiophobia maintain bracing or minimizing of trunk movements in avoidance of feared pain, essentially doing any rapid movements with their back and head. This is the first step for a movement based digital biomarker in CLBP, but there are at least three steps needed to improve confidence in the measure. First, replication with larger population is necessary, followed by extension to different interventions, especially non-VR, and in different clinical groups. Second, the concept of velocity in this context should be further assessed. As the segmentation of the movement data was not yet based on specifically known movements (as with laboratory grade dataset), it is unclear in which movements the change can be seen better than in the others. Thus, as mentioned before, collecting data by using more precise metadata about tasks is needed. Third, the characteristics of movement data contains other opportunities than just the velocity. The velocity was chosen due to its simplicity, and because the increase of movement is a desired objective in this target population. Machine learning methods might also enable multidimensional descriptors without a specific value when analysing movement data.

The analysis of RWD in CLBP had limitations. For movement data, a linear regression slope as a measure of change over time was used. The slope was selected to aggregate the change to a single measure; but it is obviously lacking more detailed information about movements. Further research with more detailed data is needed to better quantify the different aspects of movement over time. The problems with EDA were already discussed. Based on earlier studies, it is a promising method, but as discussed earlier, because it is relative to skin temperature and humidity, more data from wider population are needed (Kong et al., 2022; Koskimäki et al., 2017; Szikszay et al., 2022). The activity data analysis was not successful since it contained only aggregated daily data instead of raw data – especially heart rate variability analysis wasn't just possible with this level of accuracy. However, it has shown to be possible to measure the correlation between general activity data and chronic pain assessment (Fjeld et al., 2022). Also, it must be noted that the study population in both CLBP datasets consists mainly of female participants. Further research with both bigger populations, but also with more male participants is needed.

Longitudinal changes in movement over time appears to be potential area for a clinically meaningful digital biomarker to be exploited in intervention studies aimed at the rehabilitation of adults with CLBP. The potential exploitation of these digital biomarkers does not necessarily have to be limited with the clinical trial data collection or the treatment optimisation in the traditional way. As the narrative of

this thesis has been very much focused around the research and development of DTx, the opportunity to exploit digital biomarkers can also be seen in this modality. In the future we will see more and more automatically adjusting and personalised DTx solutions, where the level, complexity, and difficulty of interventions, especially when talking about gamified approaches are automatically adjusted for individuals (personalised treatments). An example of this is Cognoa's DTx for autism spectrum disorder (Megerian et al., 2022). Their method combines a caregiver questionnaire, analysis of two short home videos, and an HCP questionnaire with a gradient boosted decision tree machine learning algorithm to produce either an ASD positive, ASD negative, or indeterminate output. One possible arrangement of collection, analysis, and adjustment of VR experience by using the wearable data and VR technology is shown in **Figure 32**. By using the methods and analytical techniques researched in this work, it is already possible to create a closed-loop process control for digital treatment optimisation.

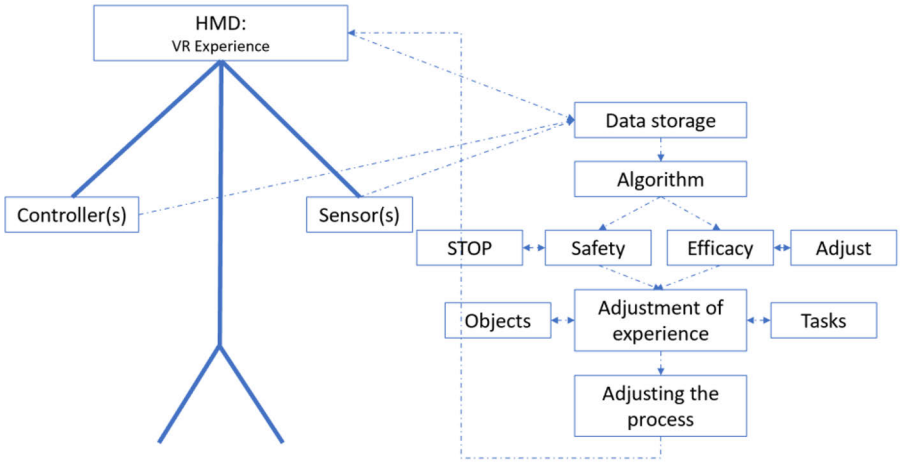

Figure 32. Possible arrangement on the collection, analyses, and exploitation of the movement data in adjusting the experience in VR based treatment.

Compared to CP, the research of novel digital diagnostic methods and biomarkers is more advanced in PD. The exploitation of wearables and hardware specifically designed for this in the detection of motor symptoms is not new (Chen et al., 2020; Rissanen et al., 2021). Furthermore, the use of commercial wearables in the diagnosis of PD onset, and in the detection of motor symptoms is active and already in clinical use. StrivePD by Runelabs is an example of FDA cleared solution for PD which measures tremor and dyskinesia, tracks medication use, adverse

events, and patient-reported outcomes such as mood and overall health with PD patients with DBS devices (Larkin, 2022). The full potential of commercial wearables in the automatic detection requires still more research though some promising methods have been suggested (Bloem et al., 2023; Joshi et al., 2019). Mainly this is due to the challenge in detecting the motor symptoms from the extremely noisy RWD. It is difficult to separate the symptoms from the everyday activity in all its nuances. The case with non-motor symptoms in PD, and as with the CP, is more difficult. These are always personal experiences, and difficult to measure with wearables without asking the patient to constantly report the well-being. This is also something that is still partially the problem with the motor symptom detection. The difference between perceiving the symptoms and observing the symptoms is existing even with motor symptoms, but obviously more so with non-motor symptoms, as this can't be observed but must be reported by the patient. Also, as PD is a chronic disease, many of the available solutions are not engaging users and thus the compliance in the longer-term use is challenging. It seems that many of the solutions are designed for the physicians, and not for the patients, as is with Parkinson's KinetiGraph (Guan et al., 2021). Patient wears the device for a certain period, but the analysis goes to the neurologist, not to the patient. The immediate reward for using the device is missing. There is still unmet need in the field of digital solutions for PD. In this thesis a novel method for the analysis of movement state before motor symptom detection was found. Also, a novel and usable method for the collection of data for symptom analysis based on subjective assessment was reported.

The research in PD between laboratory and real-world grade data was done more simultaneously and iteratively. The analysis of the laboratory grade data in PD (Levodopa Response Study data by MJFF) showed that a movement state can affect the visibility of PD symptoms, as reported earlier (Daneault et al., 2021). Thus, the quantification of PD symptoms is highly dependable on the movement states. Additionally, it was discovered that the unsupervised variational autoencoders (VAEs) can make it relatively easy to estimate movement states. Because of this dataset and its analysis, the findings with the real-world accelerometer data were made possible. A great proof that the facilitation of the research in PD by MJFF has an impact.

In the **Figure 33** is illustrated one potential high-level arrangement on how the data analysis of PD symptoms, after the detection of movement state could be organised. Note that when the movement state is known (e.g., person is doing a specific and known physical task), no movement state analyses is needed to quantify PD symptoms within this special movement state.

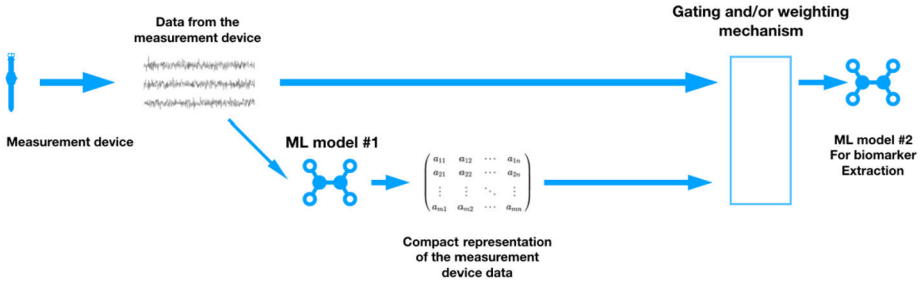

Figure 33. Possible arrangement of wearable data in the detection of PD symptoms. The wearable data is divided into known (arrow above) and unknown (lower arrows) movement states. The known wearable data is quantified (ML model #2) straight for PD symptoms. The unknown wearable data is first analyzed for its movement state (ML model #1) before the symptoms are quantified (ML model #2).

The design and usability of the RWD collection arrangements by using a commercial wearable device and a bespoke mobile application were found to be good enough for the purpose. Vast majority of participants assessed wearing the device an entire day easy enough, the reminders helpful and the symptom recording easy enough. Reporting symptoms when they occurred instead of after the symptoms has disappeared was a thing that needs to be improved for the future as most of the symptoms were reported retrospectively. This also had a negative impact on the data analysis, the accuracy of retrospective reporting is naturally lower compared to live reporting. The median age of participants was rather low, which can be seen as a limitation in the usability results. Though no age-related usability difficulties were observed nor reported, which suggests older people are also able to use wearable and mobile devices. Also, the upper limit of age in the inclusion criteria was set to 75 years and many interested people, even over 80 years old, were excluded from this study due this limitation. The usability of eHealth solutions in PD and other chronic indications has been studied earlier with results (Bendig et al., 2022; Keogh et al., 2021), but it seems many of the usability studies are more concentrating on the ability to use the arrangements correctly, instead of more difficult perspective: the engagement. Many of the devices and apps in PD are designed to function well in what they are aiming to do, but it is often forgotten that users should be kept engaged over long periods of time. Many of the solutions offer very limited benefits back to the patients. It is important that they are given both something useful back for using the wearable and treatment compliance apps. Various digital treatment therapies such as physiotherapy, speech therapy and psychotherapy might motivate the people with PD in using the solution over the weeks, months, and years with progressing and fluctuating PD.

Here, more than 7000 symptom events were reported by patients with the app, showing the potential for data collection method. Combining the event reports with the accelerometer data from a commercial device opens possibilities for understanding symptoms and improving medication and overall care.

Having a solid reference for the symptoms is important in collecting data for supervised models. Compared to situations where the models already exist, collecting data requires a more comprehensive design and can be more challenging for participants. In this context, it's crucial to have accurate records of symptom diaries and evaluations, but this has shown to be difficult even with video recording and training (AlMahadin et al., 2020; Sibley et al., 2021). It's also unclear what should be used as a control when trying to identify time slots where symptoms occur. For instance, as movements don't usually occur during sleep, the sleep needs to be detected and removed before the analysis of movement data in daytime is possible. Unless the analysis of movement during the sleep is the objective. Additionally, potential confounders such as technical issues like device wearability and data quality must be considered. Using unsupervised models to identify movement states won't solve these problems.

The symptom quantification modeling pipeline was relatively straightforward, involving power spectra of blocks followed by linear models or generalized linear models (GLM). We found that symptom types had characteristic spectral shapes that replicated across data sets and had rather broad temporal envelopes. This suggests either long-duration symptoms or low temporal resolution of symptom diaries based on our own data collection. No accelerometer channel, including the derived virtual channels, seemed to be superior to another, except for low tremor amplitude in the direction of the limb. In our analysis, we used blocks of 21.8 minutes, except for VAEs. This time scale was chosen as it was similar to the time scale of reported symptoms in diaries, typically tens of minutes. Much shorter intervals would be more useful when dynamically detecting symptoms from raw data. Spectral resolution would be sufficient even in ten-second blocks, the temporal scale used in the VAE.

As seen with the simple models from accelerometer signal, MJFFd shows attenuation of bradykinetic, and amplification of dyskinetic signals in some fine-motor tasks, and bradykinesia also while walking (Daneault et al., 2021).

The primary objective of the RWD study was the identification of OFF symptoms, as perceived by the subject, with reasonable accuracy from RWD collected with commercially available Garmin Vivosmart 4 wearable device and a mobile application. With motor symptoms such as tremor, bradykinesia, and dyskinesia the findings are promising, matching also with findings in MJFFd. Similar results with specifically tailored wearables have been reported, even with gait (Burq et al., 2022; Powers et al., 2021). For the commercial wearables containing an accelerometer, more research with larger populations and improved

methods in collecting the data is still needed. While the full potential was not shown with limited dataset, with more patient data, one should be able to train models to detect useful movement states, and then use e.g., supervised models to quantify symptoms from chosen periods. Efficient model development may require a data collection arrangement that has both unknown and known periods of activity in it. Generalizability to clinical populations requires a larger patient sample than what was available in this research (Powers et al., 2021).

The studies in this thesis were all done by using DTx solutions under development. In CP, the solutions were all VR based. Even with VR as the vehicle, more data and research are needed before the found signals in this thesis can be developed into validated biomarkers. The other well-known clinical studies on VR treatments are all collecting and reporting clinical outcomes only, so even with VR the research of digital signals is still very young (Garcia, Birckhead, Krishnamurthy, Sackman, et al., 2021). Measuring wearable data (e.g., movement, HRV) in clinical trials in CP and PD should be almost a pre-requisite when assessing the outcomes with patients in real life. Furthermore, there is a huge opportunity in expanding the use of these signals and biomarkers for the use cases that do not use VR. The analysis of longitudinal movement data from CP patients in general, when proven to be correlated with clinical endpoints, would enable more insights about the well-being and condition of them. This would help the healthcare professionals and even patients, by offering them a more comprehensive snapshot about the patient's condition and wellbeing. This can be then used in optimising the treatment more efficiently and even remotely.

In PD more research is needed to test the efficacy of the movement state analysis before the symptom detection analysis. It would be interesting to see how much better the symptom detection with pre-analysis of movement data can be. Furthermore, as the fluctuation of PD symptoms is a common problem in the advanced disease stage, the future development of automatic and passive symptom detection into a pharmacodynamic model opens the opportunity of adjusting the medication almost in real-time. That would require connecting the digital pharmacodynamic model into population level pharmacokinetic / pharmacodynamic model of the medication (e.g., levodopa and the levodopa equivalent models).

Also, it would be interesting to compare how the two different pre-analysis models here, HMM and VAE, would perform against each other in PD and CP, and vice versa. They were both used in the pre-analysing of the movement data, before the actual analysis, and there is no reason why they wouldn't be able to do the job in the other indications that have manifest with motor symptoms as well. And as discussed earlier, this manifestation can be also as subtle as with the eye-movement.

Overall, there are some clear opportunities for digital biomarkers for motor symptoms in both CP and PD. Interestingly, tremor is intuitively easy to understand

as a motor symptom in PD. The erratic and not so easily detectable everyday movements are a similar opportunity in CP in the future. And there are also similarities in how the pain is perceived in CP, and how the non-motor symptoms are experienced in PD. So, automatic detection of motor symptoms is an opportunity for both CP and PD. As for the non-motor symptoms, when the patient is unable to report or communicate the experience of the symptom, or when there is need to follow the well-being remotely, surrogate measurements as digital biomarkers is an opportunity for the healthcare in the future.

7 Summary/Conclusions

The aim was to study the usability and feasibility of RWD from wearables, mobile devices, and patients in exploring digital biomarkers and endpoints for therapeutic purposes in ND indications: more specifically in CLBP and PD. The key hypothesis was that by using commercially available wearables and mobile devices with patients in real world allows us to measure, analyse and detect clinically valid digital signals. The research was done by using a conceptual approach by collecting both laboratory grade data and RWD in both indications.

In the research of the laboratory grade CLBP data, the classification of the CLBP patients and the healthy controls with the movement data collected by using a VR program was possible with a high accuracy. It was also possible to divide the movement data into useful segments for the further analysis by using hidden Markov models.

By using the real-world grade CLBP data, collected in a randomized clinical trial of a VR based digital intervention, a novel digital signal for use in monitoring the efficacy of that intervention in adults with CLBP was found. In the future this signal could be further validated as a movement based digital biomarker to be used as a surrogate or additional endpoint in studies and treatment of chronic musculoskeletal pain.

The research with laboratory grade PD dataset from MJFF led into a VAE model that was able to detect different movement states. A pre-detection of these states with a VAE from accelerometer data followed by the quantification of PD symptoms was found to be a feasible strategy for the future.

The usability of the RWD collection method by using wearable device and mobile app and patient reported outcomes straight from the PD patients was found very promising.

Combining both the usability and the data science learnings in the future enables the development of both digital tools and biomarkers for PD clinical trials and treatment.

The research was done by using a two-phased conceptual approach. Using laboratory grade data makes the exploration and development of analytical methods for RWD easier, as it is more systematically collected and better annotated. Once the

characteristics and features of the sensor data in laboratory settings are more understood, the analysis of more volatile and noisier RWD becomes a lot easier. This doesn't mean that one could not be successful e.g., by using neural networks straight with RWD, in case no laboratory grade data or insights are available, but the journey can be a lot more difficult and require much larger datasets.

Furthermore, a stepwise, data scientifically transparent, and easy to explain development and validation of digital biomarkers and endpoints is advisable until time being. The patients, healthcare professionals, and regulators are key stakeholders here and to gain their full trust and buy-in is critical.

In the future automatic detection of motor symptoms as defined by the patients themselves, and the use of surrogate digital biomarkers such as movement, heart rate variability, skin conductance and sleep in combination with self-reported non-motor symptoms is an opportunity for the future research and healthcare.

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Sammeli Liikkanen

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