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Knee function, knee proprioception and related brain activity following anterior cruciate ligament injury

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“We learn wisdom from failure much more than from success. We often discover what will do, by finding out what will not do; and probably he who never made a mistake, never made a discovery.”

/Samuel Smiles

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Abstract

Background: Injury of the anterior cruciate ligament (ACL) may have negative effects on the short- and long-term function and proprioception of the knee joint. However, existing tests of knee function are often sports-related and less relevant for assessment in the very long term and there remains no 'gold standard' test of knee proprioception. A growing body of research also suggests neuroplasticity post-ACL injury, but brain response to lower limb proprioception tasks is not established and nor is the potentially related impact of ACL injury. Developing standardised, reliable and valid tests of knee function and proprioception including brain imaging may target rehabilitation interventions more efficiently.

Methods: Paper I assesses knee function ~23 years after ACL injury. One ACL-injured group treated with physiotherapy only (ACLD) and one with additional reconstruction (ACLR) were compared to asymptomatic controls for performance and knee kinematics of the One-leg rise (OLR) test. Paper II is a published protocol for Paper III, which is a systematic review and meta-analysis of the psychometric properties (PMPs) of knee joint position sense (JPS) tests among individuals with ACL injury. Paper IV describes the development of one weight-bearing (WB) and one non-weight-bearing (NWB) knee JPS test using motion capture. Test-retest reliability is assessed and errors are compared between an active ACLR group (~23 months after reconstruction) and two asymptomatic groups of different activity levels. Paper V characterises brain response to a knee JPS test using simultaneous functional magnetic resonance imaging and motion capture among individuals ~2 years after ACL reconstruction and controls.

Results: ACLD performed significantly fewer repetitions of the OLR with both legs compared to controls and displayed significantly greater knee abduction than ACLR and controls. Meta-analyses found sufficient validity for existing knee JPS tests, particularly those of passive movements, by showing that ACL-injured knees produce significantly greater absolute errors than contralateral asymptomatic knees and those of controls. However, the tests were found not to be responsiveness to intervention and the remaining PMPs, such as reliability, require more evidence to better determine their quality. The novel knee JPS tests of paper IV showed mixed reliability but were better for the WB compared to the NWB test and when absolute rather than variable error was the outcome measure. Post-hoc comparisons revealed significantly greater errors for less-active controls compared to the ACLR group. For Paper V, the knee JPS test recruited brain regions such as the parietal cortex, precentral gyrus and insula. Greater knee JPS errors were correlated with greater activation in the insula, as well as the anterior and middle cingula. The ACLR group showed significantly greater response compared to controls for mainly the precuneus, but only at the uncorrected level.

Conclusions: Knee function may be negatively affected more than two decades after ACL injury based on performance and knee kinematics of the OLR test, which offers a clinician-friendly assessment tool of lower limb function but requires further investigation. Existing knee JPS tests seem to discriminate ACL-injured from asymptomatic knees. Passive tests produce greater differences, but current methods are diverse and often poorly reported, complicating recommendation of specific tests for research or clinics. The novel WB and NWB knee JPS tests should be developed for improved reliability, but their outcomes demonstrate the importance of considering activity level when comparing knee JPS between groups, which is rarely done. Brain regions recruited during our knee JPS test have previously been associated with, e.g. stepping motions, interoception and body representations, confirming proprioceptive demands of the task. Correlations between knee JPS errors and response in the insula and cingula suggest they have an important role during such tasks. Subtle differences in brain response between ACLR and CTRL warrant further investigation.

Svensk sammanfattning

Bakgrund: Främre korsbandsskada (ACL-skada) har negativa effekter på knäledens funktion och proprioception (ledkänsla) även på lång sikt. Befintliga tester av knäfunktion är dock oftast direkt idrottsrelaterade och därför mindre relevanta för bedömning upp i högre ålder och/eller flera år efter skadetillfället. Vidare saknas konsensus gällande vilket som är det bästa sättet att utvärdera knäproprioception. En rad studier tyder även på förändrad hjärnaktivitet efter ACL-skada. Hjärnans aktiveringsmönster vid uppgifter som utmanar proprioceptionen i nedre extremiteterna är dock inte fastställd, inte heller hur detta aktiveringsmönster eventuellt påverkas efter en ACL-skada. Standardiserade, reliabla och valida tester av knäfunktion och proprioception med samtidig hjärnavbildning skulle kunna bidra till ökad kunskap som på sikt möjliggör utvecklingen av mer riktade och därmed effektivare rehabiliteringsinsatser.

Metoder: Studie I undersöker knäfunktion ~23 år efter ACL-skada hos personer som hade rehabiliterats med enbart fysioterapi (ACLD), alternativt behandlats med fysioterapi i kombination med ACL-rekonstruktion (ACLR). Deltagarna utförde ett uppresningstest på ett ben (One-leg rise [OLR] test). Antalet uppresningar och knäkinematiken (genom tredimensionell rörelseanalys) jämfördes mellan de ACL-skadade och ålders- och könsmatchade knäfriska kontrollerna. Studie II är ett publicerat protokoll för Studie III, vilken är en systematisk litteraturöversikt och metaanalys av befintliga ledpositioneringstester (joint position sense [JPS] tests) för utvärdering av knäproprioception hos ACL-skadade personer. Studie IV utvecklar och utvärderar, med hjälp av kinematik, ett viktbärande och ett icke-viktbärande JPS-test för knät. Reliabiliteten utvärderas och positioneringsfelen jämförs mellan en aktiv ACLR-grupp (~23 månader efter rekonstruktion) och två knäfriska grupper med olika aktivitetsnivåer. Studie V undersöker hjärnans aktiveringsmönster under ett JPS-test för knät med samtidig funktionell magnetavbildning (fMRI) och kinematik hos ACLR-individer (~2 år efter rekonstruktion) samt knäfriska kontroller.

Resultat: ACLD-individer utförde bilateralt signifikant färre uppresningar under OLR testet jämfört med kontrollerna samt visade även signifikant större knäabduktion än kontroller. ACLR-gruppen skiljde sig inte från knäfriska kontrollerna. Metaanalyser visade på tillräcklig validitet för JPS-tester i knät då individer med ACL-skada har signifikanta större absoluta fel med sitt skadade ben i jämförelse med det kontralaterala, icke-skadade knät samt i jämförelse med knäfriska kontroller. Detta var särskilt tydligt för tester med passiva rörelser. Däremot visade sig testerna inte vara tillräcklig känsliga för att mäta eventuella effekter av interventioner. En brist på studier av hög kvalité försvårade bedömning av andra aspekter, såsom t.ex. reliabilitet. Våra nya JPS-tester som presenteras i Studie IV visade blandad reliabilitet, men den var högre för det viktbärande jämfört med det icke-viktbärande testet, samt för utfallsmåttet absolut fel jämfört med variabelt fel. Post-hoc-jämförelser visade signifikant större ledpositioneringsfel i knät för kontroller med lägre aktivitetsnivå jämfört med ACLR-gruppen. En vidareutvecklad version av det icke-viktbärande testet aktiverade hjärnområden såsom parietalcortex, precentrala gyrus och insula. Större absoluta knäpositioneringsfel korrelerades med högre aktivering i insula, såväl som i främre och mellersta cinguli. ACLR-gruppen visade signifikant större aktiveringsgrad jämfört med kontroller för huvudsakligen precuneus, men bara på okorrigerad nivå.

Slutsatser: Knäfunktionen kan fortfarande vara nedsatt mer än två decennier efter ACL-skada baserat på utförande och knäkinematik vid OLR-testet. OLR-testet kan komma att utvecklas till ett användbart kliniskt test för bedömning av nedre extremitetens funktion efter korsbandsskada i olika åldersgrupper. Befintliga JPS-tester för knät, särskilt de med passiva rörelser, verkar särskilja ACL-skadade från friska knän. Metoderna är dock olika och ofta otillräckligt rapporterade, vilket komplicerar rekommendationerna av specifika tester för forskning och klinik. De nya JPS-testerna som utvecklats för utvärdering av proprioception i knät bör utvecklas ytterligare för förbättrad reliabilitet. Resultaten visade på vikten av att i högre utsträckning beakta aktivitetsnivå vid jämförelser mellan grupper. De hjärnområden som rekryterades under JPS-testet har tidigare associerats med exempelvis sensorimotoriska processer samt fokusering på kroppspositioner och kroppsuppfattning, vilket verkar bekräfta att uppgiften ställer krav på proprioceptionen. Större knäpositioneringsfel var till och med relaterat till högre grad av aktivitet i den främre och mellersta cinguli såväl som insula, vilket tyder på att dessa hjärnområden har en viktig roll i samband med knäpositioneringsuppgifter. Subtila skillnader mellan ACLR och CTRL, framförallt för precuneus, bör undersökas vidare.

Abbreviations

The abbreviations below are found in the main text.

ACL	Anterior cruciate ligament
ACLD	Anterior cruciate ligament-deficient (treated without surgery)
ACLR	Anterior cruciate ligament-reconstructed
AE	Absolute error
AM	Anteromedial
ANOVA	Analysis of variance
ATHL	Asymptomatic elite athletes
BMI	Body mass index
BOLD	Blood-oxygen-level-dependent
CE	Constant error
CNS	Central nervous system
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CTRL	Asymptomatic controls
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
ICC	Intraclass correlation coefficient
JPS	Joint position sense
L-ACLR	Left-side anterior cruciate ligament-reconstructed persons
LSI	Limb symmetry index
MD	Mean difference
MDC	Minimum detectable change
MRI	Magnetic resonance imaging
NWB	Non-weight-bearing
OLR	One-leg rise
PL	Posterolateral
PMP	Psychometric property
R-ACLR	Right-side anterior cruciate ligament-reconstructed persons
RoB	Risk of bias
RTS	Return to sport
SD	Standard deviation
SEM	Standard error of measurement
SMD	Standardised mean difference
VE	Variable error
WB	Weight-bearing

Original papers

This thesis is based on the following original papers. They will be referred to in the text by their respective Roman numerals.

I. Strong A, Tengman E, Srinivasan D, Häger CK. One-leg rise performance and associated knee kinematics in ACL-deficient and ACL-reconstructed persons 23 years post-injury. *BMC Musculoskeletal Disorders*. 2019;20:476.

II. Arumugam A, Strong A, Tengman E, Röijezon U, Häger CK. Psychometric properties of knee proprioception tests targeting healthy individuals and those with anterior cruciate ligament injury managed with or without reconstruction: a systematic review protocol. *BMJ Open*. 2019;9(4):e027241.

III. Strong A, Arumugam A, Tengman E, Röijezon U, Häger CK. Psychometric properties of knee joint positions sense tests targeting individuals with anterior cruciate ligament injury: A systematic review and meta-analysis. (Submitted)

IV. Strong A, Srinivasan D, Häger CK. Development of weight-bearing and non-weight-bearing knee joint position sense tests among anterior cruciate ligament-reconstructed and asymptomatic persons. (Submitted)

V. Strong A, Grip H, Boraxbekk C-J, Selling J, Häger CK. Functional brain response during a knee proprioception test among individuals with anterior cruciate ligament reconstruction and controls. (Manuscript)

Thesis at a glance

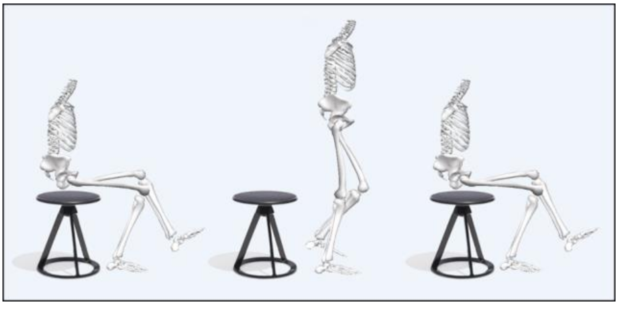
Paper I. Performance of the One-leg rise test on average 23 years after ACL-injury (treated with [ACLR] or without [ACLD] surgical reconstruction) compared to age- and sex-matched controls. Outcome variables of performance (repetitions and time) and knee kinematics (abduction/adduction and movement units). Cross-sectional study.

Groups:

ACLR, n = 33

ACLD, n = 37

Controls, n = 33



Paper II. Protocol for systematic review and meta-analysis of the psychometric properties of knee proprioception tests targeting asymptomatic individuals and those with ACL injury.

Paper III. Systematic review and meta-analysis of the psychometric properties of knee joint position sense tests targeting individuals with ACL injury.

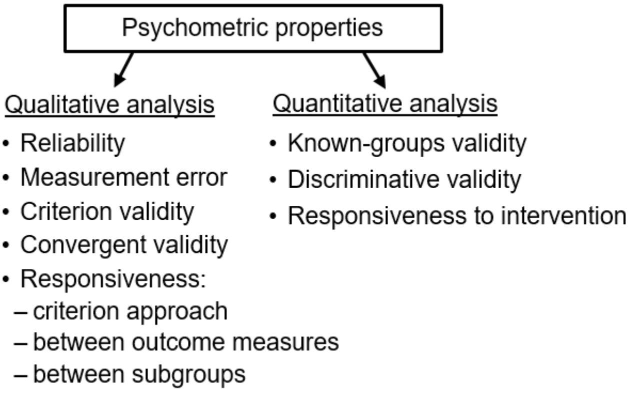
Included:

Studies = 80

Knee JPS tests = 119

Participants = 2475

ACL groups = 112



Paper IV. Development of two novel knee JPS tests (one weight-bearing and one non-weight-bearing) among asymptomatic controls and ACL-injured individuals on average 23 months after surgical reconstruction (ACLR). Assessment of test-retest reliability, known-groups validity and discriminate validity. Cross-sectional and test-retest study.

Groups:

Test-retest reliability

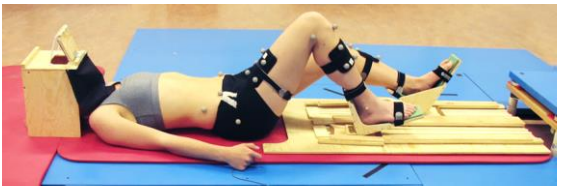
Controls, n = 24

Discriminative analyses

ACLR, n = 18

Less-active controls, n = 23

Activity-matched athletes, n = 21



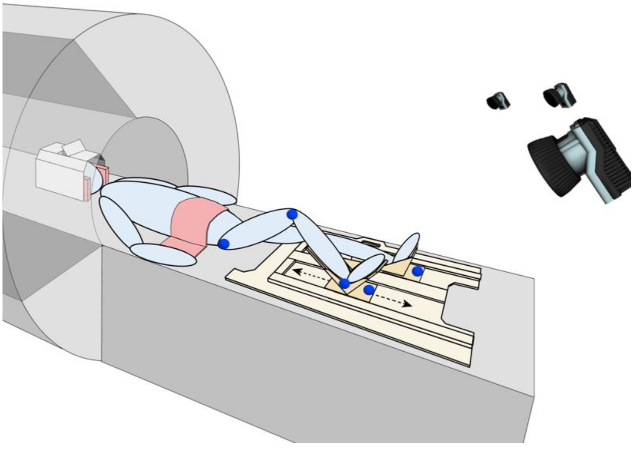
Paper V. Assessment of brain response to a knee JPS test using fMRI and simultaneous motion capture. Effect of ACL-reconstruction (on average two years after surgery [ACLR]) and correlation analysis between knee JPS errors and brain response. Cross-sectional and test-retest study.

Groups:

Left-side ACLR, n = 11

Right-side ACLR, n = 10

Controls, n = 19



Preface

I have long been interested in physiology, anatomy and biomechanics. At the age of 15 I began working as a gymnastics coach and fitness instructor. Several years later I then studied a Sport Science degree at Kingston University, London. I had however applied for the Physiotherapy programme at Umeå University, knowing that my lack of Swedish language skills made me ineligible. After completing my degree and working for two more years at Kingston as a biomechanics technician, I moved to Umeå and searched for opportunities to make use of my degree. Luckily, an advert for a position at the physiotherapy department of the University required experience of the equipment I had been working with in England. Even better, the research area was knee injuries, a subject I became interested in during my undergraduate degree. Unfortunately, it was a post-doctoral role and I wasn't qualified. Undeterred, I sent an email to the contact person, Charlotte Häger, to enquire about other possibilities. Charlotte invited me to meet her the following week, which led to a research assistant position and a master's degree in physiotherapy. Fifteen years after my unsuccessful attempt to enter the undergraduate programme, I am so grateful to have been given the opportunity to study as a doctoral student in physiotherapy at Umeå University.

This thesis focuses on the functional, proprioceptive and neuroplastic effects of anterior cruciate ligament (ACL) injury. Despite vast amounts of research into risk reduction and treatment strategies, ACL injuries remain common in many sports and require a long period of rehabilitation before return to activity is recommended, if at all. Long-term consequences, such as early-onset knee osteoarthritis, can also reduce quality of life in to older age. For the original papers included here, three-dimensional motion capture systems provided kinematic data for movement analysis and real-time feedback. For the final paper, additional functional magnetic resonance imaging (fMRI) provided brain imaging data. Knee function was assessed two decades after ACL injury based on performance and kinematics of the One-leg rise test. A systematic review with meta-analyses assessed the psychometric properties of existing knee joint position (JPS) sense tests among individuals with ACL injury. Novel weight-bearing and non-weight-bearing knee JPS tests were developed and outcomes were compared between ACL-reconstructed and asymptomatic knees. Brain response to a novel lower limb JPS test was also investigated using motion capture and simultaneous fMRI. The introduction of this thesis provides an overview of the ACL before focusing on related proprioception and neuroplasticity. With this research I hope to build on existing evidence relating to the long-term effects of ACL injury on knee function as well as the growing body of literature related to proprioception and neuroplasticity post-ACL injury.

Introduction

The human knee and anterior cruciate ligament

Anatomy and function of the knee

The knee is classified as a gliding hinge joint, or trochoginglymos.[1] It is capable of movement in six degrees of freedom; three rotations and three translations.[1-5] Rotations are produced by flexion/extension, adduction/abduction, and internal/external rotation. Translations occur anteriorly/posteriorly, medially/laterally, and by distraction/compression (Figure 1).[1, 5, 6] The four main ligaments of the knee are the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), the medial collateral ligament (MCL) and the lateral collateral ligament (LCL).[1] All of the four ligaments are defined as passive stabilisers of the knee, as opposed to active or dynamic stabilisers such as the muscles crossing the joint.[7, 8] However, despite the 12 different directions in which the knee can move, there is relatively limited range of motion for all but flexion/extension.[6]

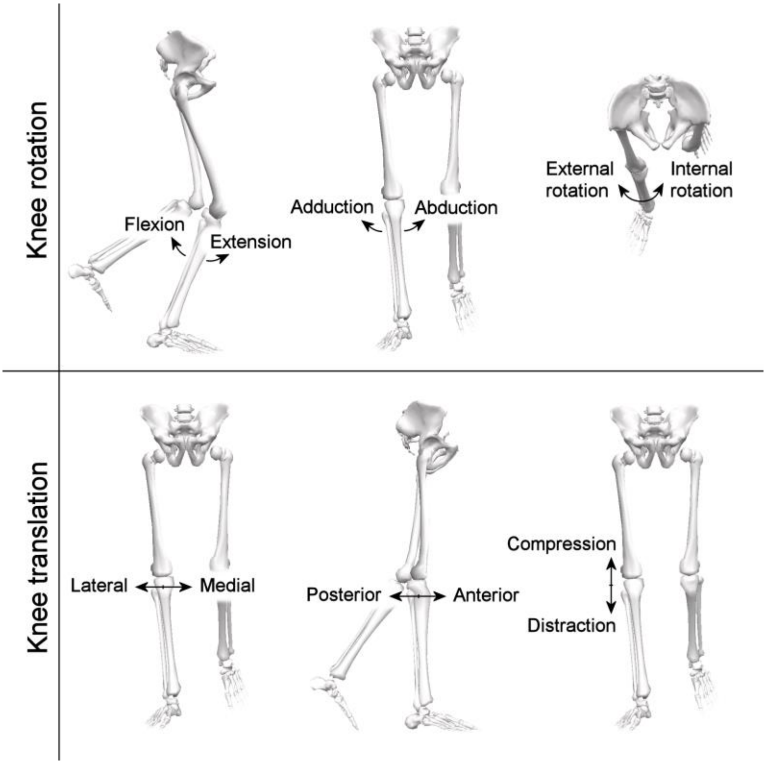


Figure 1. Illustrations of the six degrees of freedom at the knee joint showing three rotations and three translations.

Anatomy and function of the ACL

The ACL plays a particularly important role in stabilising the knee joint.[9] It attaches proximally to the posteromedial surface of the lateral femoral condyle and distally to the anterior intercondylar fossa on the tibial plateau.[10, 11] Its main function is to resist anterior tibial translations and, to a lesser extent, rotational loads particularly near full extension.[10, 12] It is commonly divided into two functional bundles, named the anteromedial (AM) and posterolateral (PL), with their terminology implying the location of their respective tibial attachment sites.[12-14] It has been proposed that these two bundles have distinctly differing functions and properties. For example, the AM bundle appears to have more strongly aligned collagen fibres when loaded and is thus stronger/stiffer than the PL bundle.[15] Also, the PL bundle appears to become taut during knee extension but lax during knee flexion, with the opposite true for the AM bundle.[8, 13, 14, 16] Thus, the two bundles complement each other by providing stability to the knee joint throughout its full range of motion.[11] However, the ACL is a complex structure which comprises of many fibres and subdividing simply into these two bundles remains controversial.[17] Some cadaveric studies have identified three separate bundles,[16, 18] whereas other studies have preferred to classify the ACL as a continuum of multiple bundles.[15, 19, 20] Functionally, however, these alternative anatomical distinctions are not believed to be differentiated and thus the dichotomous division of the AM and PL bundles remains the most relevant.[2]

Neural elements of the ACL

The ACL consists of neural elements covering approximately 1-2.5% of its area.[21, 22] These neural elements are sensory receptors commonly referred to as mechanoreceptors. Mechanoreceptors provide specific afferent information to the central nervous system (CNS) depending on their location and characteristics.[23] Classification of the different types of joint mechanoreceptors is controversial partly due to the differing methods used to observe them, as well as the difficulties in distinguishing their often polymodal functions.[23] Nevertheless, a number of different mechanoreceptors have been shown to exist in the ACL and are commonly classified in accordance with Freeman and Wyke[24] as either slowly or rapidly adapting. Slowly adapting mechanoreceptors show continuous activity in response to changes in motion, position and rotation angle of the joint.[11] Examples of such slowly adapting mechanoreceptors in the ACL are Ruffini endings and Golgi tendon-like receptors.[10, 22, 25, 26] The rapidly adapting mechanoreceptors on the other hand, such as Pacinian corpuscles, are more sensitive in detecting changes in tension in the ligament and identify acceleration regardless of joint position.[10, 11, 22, 26] Free nerve endings are also abundant and mainly serve as nociceptors to signal pain, but are widely believed to contribute as high-threshold mechanoreceptors.[21-23] Although the clinical significance and functional relevance of these neural elements remains unclear, these many sensory endings of the ACL suggests that it has a proprioceptive function.[8]

Proprioception

Charles Sherrington was the first to use the term "proprioception" when describing muscular receptivity.[27] Riemann and Lephart[28] have since defined proprioception as "afferent information arising from internal peripheral areas of the body that contribute to postural control, joint stability, and several conscious sensations". Proprioception thus includes several senses such as force, effort, movement, and limb position, at an intrinsic level arising from stimulus of receptors within the body.[29] The central nervous system (CNS) processes this afferent information at three levels: 1) the spinal level, 2) the brain stem, and 3) the higher brain centres.[30] Proprioception is an important aspect of sensorimotor control regarding both feedforward and feedback control of motor commands.[31] Its importance to how we perform movements and interact with our environment is most starkly evident in rare cases of deafferented individuals who lose their sense of proprioception on a whole-body scale.[32-34] Proprioception is fundamental in the intra- and inter-limb coordination of movement and posture, which are both critical for preventing injuries.[35] Indeed, decreased proprioceptive acuity is believed to contribute to non-optimal coordination which exposes the body to positions of heightened injury risk.[36] The receptors involved in proprioception are located in muscle, skin and the joints.

Muscle receptors

The receptors located in the muscles are widely believed to provide the most important contributions to proprioceptive sensations.[29, 37] Specifically, muscle spindles are sensitive to stretch and can provide information regarding the amount and rate at which a muscle changes length.[28, 38] For a comprehensive overview of the functional properties of muscle spindles, the reader is directed to a recent article by Macefield and Knellwolf.[37] Briefly, muscle spindles are striated, intrafusal muscle fibres, the majority of which are located in the muscle belly.[37, 39] They consist of bag 1 and bag 2 fibres, as well as the smaller nuclear chain fibres.[29, 38] Bag 1 fibres are classified as dynamic because they respond maximally to the velocity of change in muscle fibre length.[38] Bag 2 and nuclear chain fibres, on the other hand, are classified as static because they respond maximally to the amount of stretch in the muscle fibre.[38] The position of the muscle spindles parallel with the fascicles of the extrafusal muscle fibres means that changes in muscle length result also in the modulation of the intrafusal fibres.[37] Such changes in length are detected by receptors of the muscle spindles.[37] Afferent impulses from these receptors are subsequently carried along fast-conducting primary (type Ia) axons and slower-conducting secondary (type II) axons to the CNS.[37, 39] The type Ia axons innervate all three muscle fibres, whereas type II axons innervate only bag 2 and nuclear chain fibres.[37] It is believed that the type Ia primary endings contribute with the senses of position and movement, whereas the secondary type Ia endings contribute only with the sense of position.[40, 41] For efferent innervation, bag 1 fibres are also innervated by gamma dynamic (γ dynamic) motor neurones, whereas bag 2 and nuclear chain fibres are innervated by gamma static (γ static) motor neurones.[29, 37, 42] Additionally, fast-conducting alpha (α) motor neurones innervate extrafusal muscle.[39] The γ and α motor neurones subsequently drive motor function by conveying efferent signals from the CNS to the muscle.[39] This complex circuit involving afferent and efferent signals between the muscle spindles and CNS is thus essential for coordinated movement control and coordination.

Cutaneous receptors

The skin contains four different kinds of receptors thought to play a role in proprioception: rapidly-adapting Meissner corpuscles (type I) and Pacinian corpuscles (type II), and slowly-adapting Merkel endings (type I) and Ruffini endings (type II).[29, 43-45] When movements occur at the joint, the surrounding skin is either stretched or slackened and thus the receptors are thought to provide afferent information to the CNS regarding these deformations.[29, 46] The majority of studies which have found evidence for the role of cutaneous receptors in proprioception have based their findings on sensations at the hand. Several studies, for example, have found that strain on adjacent skin of the fingers causes illusions of finger movement when they are in fact stationary.[47-49] Findings from other joints, such as the elbow and knee, have also shown that manipulation of skin receptors causes inaccurate perceptions of movement.[50] Additionally, reducing feedback from skin receptors on the posterior ankle by anaesthetisation has been shown to increase errors during position matching tasks at the joint.[51] Thus, cutaneous receptors play an important role in proprioception. However, they appear to be more responsive to movement than position and their overall contribution is thought to be less than that of the muscle spindles.[29, 46]

Joint receptors

The joint capsule itself, similar to the skin, will undergo opposing stretch and compression during rotations.[29, 46] Depending on the type of rotation, ligaments will consequently also undergo deformations. Due to the presence of Ruffini endings, Pacinian corpuscles, Golgi tendon organ-like endings and free nerve endings in the joint, a role in proprioception has long been suggested.[52] Subsequently, evidence indicates that joint receptors do indeed provide afferent signals, but mainly at the extreme ranges of joint motion.[46, 53, 54] Nevertheless, evidence for their contribution to proprioception even through the mid-range of joint motion has been found.[55-57] Additionally, studies have also found greater activity of the joint afferents during movements that are active rather than passive.[58, 59] It should be noted however, that much of the evidence pertaining to joint receptors is based on animal studies, specifically in cats, and a lack of data exists for humans.[29] Nevertheless, it appears that joint receptors do indeed contribute to proprioception, but mainly towards the limits of their normal range.[29]

Injury of the ACL

Injury mechanisms of the ACL

The ACL has been reported to have an approximate maximum tensile strength of 1,725 ± 270 N.[8] It should therefore be more than capable of withstanding normal sporting situations without rupturing. Despite this, non-contact mechanisms appear to account for 70-88% of all ACL injuries.[60-63] In the majority of cases movements are typified by slight knee flexion, a dynamic knee valgus loading (distal femur moves towards and distal tibia moves away from the midline of the body[64]) and some internal or external rotation of the tibia.[60, 61, 65-67] These positions of heightened injury risk tend to occur during rapid decelerations shortly after initial ground contact from manoeuvres that involve side-cutting or landing.[67] Additionally, incidence rates are more common during competition than practice.[68] In fact, a 14-fold higher incidence rate of ACL injuries during competition matches compared to during training has been reported in the highest division of Italian football.[69] Reasons for this may include the greater mental and physical stress of competition typified by increased external attentional demands, the heightened intensity of the play, or the more vigorous physical contact in the cases of direct and indirect contact mechanisms.[68] Nevertheless, given these reports, insufficient momentary awareness of the position of the knee and/or reactive control appear to be important with regard to ACL injury risk. It remains uncertain as to whether or not fatigue is a factor with regard to ACL injury risk. A meta-analysis which included studies of a number of different team-based ball games found that neither time in season nor time in game influenced ACL injury risk.[70] Evidence suggests that ACL injuries may not simply be the cause of a one-off event, but in some instances may be the result of overuse which results in an accumulation of damage without the necessary time for recovery.[71] However, more evidence is required to support these findings.

Epidemiology of ACL injuries

Knee injuries have been found to be the most likely to end a career and the ACL as the most commonly injured structure.[72] Incidence rates for ACL injury are 68.6 per 100,000 person-years in the USA,[73] with sex and type of sport two of many decisive factors.[74] For example, the ACL injury rate per 10,000 athlete-exposures is 2.49 among females for football (soccer) compared to 0.79 for males in the same sport and compared to 0.44 for ice hockey within the same sex.[75] In fact, females are at an approximately three times greater risk for ACL injury compared to males.[75-77] The risk for a second ACL injury across both sexes has been reported to be as much as 35% over a five-year follow-up among individuals who had primary surgery at a mean age of 17.2 years.[78] Interestingly, results from the same study show similar rates for graft ruptures (18%) compared to contralateral ACL injuries (17.7%), which is supported by a previous study indicating similar rates between legs.[79] As previously mentioned, type of sport is also a contributing factor, with a return to moderate and strenuous sports requiring jumping, pivoting and side-stepping increasing the odds of contralateral ACL injury 10-fold.[79] Various preventive training programmes have been designed and implemented within certain sports with positive results suggesting their effectiveness in reducing injury risk.[80-82] A systematic review and meta-analysis indicated a decrease in ACL injury risk of 52% and 85% for females and males respectively.[83] However, although interest in performing such training programmes appears high (89%) among female college athletes in the USA, actual participation and awareness of such programmes is low (15% and 33% respectively).[84]

Treatment of ACL injuries

ACL reconstruction techniques

ACL injuries are treated with either rehabilitation alone (individuals are commonly referred to in the literature as ACL-deficient; ACLD) or with additional reconstructive surgery (ACL-reconstructed; ACLR). In the USA, reconstructive surgery is performed in approximately 80% of cases.[85] This is however not the case in all countries. In Sweden, for example, about 50-60% of ACL injuries are treated with reconstructive surgery.[86] To complicate the matter further, a number of different techniques for reconstructive surgery exist. Two main types of graft are the autograft and the allograft. An autograft involves taking tissue from the same individual, whereas an allograft involves taking a tissue or organ graft from another individual.[87] Currently, autografts are more common than allografts and have been claimed to be superior regarding graft failure, patient-reported outcomes and RTS.[88] However, a recent systematic review found a lack of significant differences between the two types based on post-operative outcomes.[87] Factors associated with surgical technique that can determine the outcomes of an ACL reconstruction include graft selection, tunnel placement, initial graft tension, graft fixation, graft tunnel motion and rate of graft healing.[8] Three of the most common ACL grafts are the hamstring, quadriceps and patella tendon.[89, 90] In Sweden and Denmark, hamstring autografts are used in approximately 90% and 80% of cases, respectively, whereas in Norway and the USA the majority are performed using patellar autografts.[86, 88]

Developing new improved surgical techniques remains an area of interest. During reconstructions, the native ACL is removed and replaced with the respective tendon graft. However, repairing the native ACL was the most common technique in the 1970s/80s. Due to negative outcomes for repair at mid- and long-term follow-ups reported in several studies at the time,[91-96] reconstruction with autograft has since become the most common surgical treatment method. Interest in repair has nonetheless persisted, mainly due to potential of preserving the proprioceptive properties of the ligament which have been suggested to improve muscular stabilisation and functional performance compared to reconstruction.[90, 97-99] Recent comparisons of these techniques in the literature are uncommon and it remains to be established whether ACL repair using modern techniques offers any favourable advantage regarding knee function and proprioception.

Physiotherapy treatment following ACL injury

Regardless of whether surgical interventions are performed, rehabilitation is always recommended and guidelines are constantly evolving based on current evidence. For example, compared to traditional strategies, modern ACL rehabilitation programmes include shorter periods of immobilisation, earlier progressions, and a greater emphasis on weight-bearing activities.[100] In fact, studies published prior to the year 2000 show RTS at a competitive level among ACL-reconstructed individuals to be only 44%, whereas after 2000 it is 56%.[101] Currently, neuromuscular training programmes are widely encouraged and have been reported to improve biomechanical outcomes and reduce incidence of knee injuries.[102-107] Such programmes are diverse but generally focus on improving sensorimotor control and proprioception, often involving equipment which provides an unstable base of support.[106] Providing specific rehabilitation guidelines is, however, far from straightforward and a recent systematic review found insufficient evidence to provide recommendations.[108] Nevertheless, current general guidelines have been proposed which emphasise progressions to phases or stages based on specific criteria.[109] In cases where surgical interventions are scheduled, preoperative therapies such as addressing potential deficits in knee extension range of motion and quadriceps strength are believed to be beneficial.[100, 108, 110] Post-operatively, or for those being treated with rehabilitation only, the physiotherapist assumes the main responsibility for decision-making regarding progressions of exercises. Such progressions take into consideration aspects such as pain, strength, range of motion, movement control and psychological readiness.[108, 110] The physiotherapist is thus responsible for continual assessment of the individual and has several tools with which to base these decisions on, such as strength, mobility and hop tests.

Knee function after ACL injury

Return to sport

Prior to surgical treatment, 94% of ACL-injured individuals expect to return to their previous activity level.[111] A successful treatment outcome for the majority of individuals could thus be considered a safe return to at least the same level. Unfortunately, a meta-analysis found that in fact only 63% return to their pre-injury activity level.[112] A number of factors positively associated with return to sport (RTS) are younger age,[113] male sex,[114] higher level of sports performance,[115, 116] better functional performance,[116] higher rating of self-reported knee function,[113, 117] greater psychological readiness,[116, 118-122] completion of a rehabilitation programme which incorporates jumping and agility exercises,[113] longer time from surgery,[123] and passing RTS criteria.[124] RTS criteria are designed to ensure that individuals are capable of performing at the desired level without an increased risk for injury compared to their peers. Three main factors have been proposed when deciding upon readiness for RTS: 1) physical readiness, 2) psychological readiness, and 3) biological healing.[109] Examples of physical and psychological readiness criteria include sufficient scores and performances related to lower extremity landing control, hopping ability, leg muscle strength, and questionnaires.[120] However, there appears to be little scientific validity for many of the widely used physical tests that are often included in RTS test batteries.[125] Of course, passing RTS criteria is no guarantee of avoiding future injuries. In fact, a systematic review and meta-analysis found that although individuals who pass RTS criteria have a 60% less risk of subsequent graft rupture compared to those who do not pass, they conversely have a 235% increased risk for contralateral ACL rupture.[126] Time since surgery is also considered an important factor for RTS outcomes and nine months is now often recommended as the minimum.[109, 125] In fact, ACL-reconstructed individuals who resume sports before nine months after surgery have been found to be up to seven times more likely to suffer a new ACL injury than those who wait at least nine months.[123] However, waiting at least a year after reconstruction before RTS may further improve outcomes given that the ligamentisation process for tendon autografts may in fact last beyond 12 months.[127]

Long-term consequences of ACL injury

Systematic reviews show that beyond 10 years, one in nine ACL-reconstructed individuals will suffer a graft rupture or clinical failure (i.e. poor scores for knee laxity assessments),[128] and that 12% will suffer a contralateral ACL tear.[129] It may be surprising therefore, that patient-reported outcomes have been found to be generally good.[130] Another systematic review found that the odds of developing knee osteoarthritis following isolated ACL injury are four times higher than for a non-injured knee.[131] These odds are further increased to six fold with concomitant meniscus lesion,[131] which has been shown to occur in approximately half of all ACL injuries.[132] Something that has been linked to the development of knee osteoarthritis is chronic knee instability in the ACL-injured knee.[133] Stability of the knee joint has been defined as its ability to remain or promptly return to proper alignment.[28] In research, it is common to assess this in detail using advanced motion capture systems. In clinics, a trained physiotherapist should also be able to identify aberrant movement patterns and design appropriate interventions. Very few studies exist which report ACL injury outcomes n the very long term, i.e. beyond 20 years. Nevertheless, one study with a mean follow-up time of 24.5 years did find that 84% of individuals were satisfied with the function of their knee, but that some experienced pain and reduced function.[134] Also, a 35-year follow-up of Olympic athletes with ACL injury found that 10 of 19 had undergone total knee replacement.[135] Previous results from our own study group, based on the participants included in Paper I of this thesis, indicate negative consequences on average 23 years after injury regarding single-limb stance,[136] physical activity level,[137] jump capacity,[137] knee muscle strength,[138] and aberrant knee kinematics during dynamic tasks.[139-142] Thus, assessments that are relevant to such older populations are warranted to identify those with poor knee function.

Assessing knee function

Defining good knee function is not a simple task. For many people, good knee function could perhaps be described simply as a knee that does not limit them from doing everyday tasks. For sportspeople however, a knee may only be considered as having good function if the individual's ability to jump, hop, or run gives them an advantage over their peers in their specific sport. Quantifying knee function is most often achieved by either patient-reported measures such as questionnaires or performance-based measures such as the number of times an individual is capable of performing a sit-to-stand movement.[143] Following ACL injury, assessments of knee function commonly involve strength tests of the muscles crossing the joint or dynamic tasks such as hop tests.[144, 145] Hop tests are considered relevant as they mimic movements that are likely to occur during many sports with a high risk for ACL injury, thus providing a relevant assessment of whether the injured knee is capable of coping with the demands of the sport. A number of hop tests appear in the literature to assess knee function, such as the one-leg hop for distance,[90, 141, 144-146] side hop,[90, 145, 147] triple hop,[146, 148] vertical hop,[140] and the crossover hop.[148] Given morphological differences between individuals, providing normative values are challenging for outcome measures of hop distance or height. Instead, the limb symmetry index (LSI) is commonly used to compare performance of the injured side to that of the contralateral asymptomatic side.[145, 146, 148-150] The LSI is most often provided in percent and is thus calculated as: (injured side performance/contralateral side performance) ×

100. Although there have been slightly different recommendations in the literature, an LSI of > 90% has previously been suggested as sufficient regarding both strength and hop tests.[145, 151-153] However, measuring only hop distance, for example, fails to detect potential kinematic and kinetic deficiencies which reflect movement control.[144, 154] In fact, evidence suggests that LSI overestimates knee function.[149] This is because negative consequences are believed to affect even the non-injured contralateral knee of individuals with unilateral ACL injury. This is supported by evidence of deficits in the contralateral limb regarding hopping and jumping performance and kinematics[155] as well as balance during a single-leg squat.[156] Additionally, deficits in proprioceptive acuity have been suggested in the non-injured contralateral knee[157-159] and this is supported by evidence from comparisons to controls.[159-163]

The central nervous system in relation to the ACL

Knee proprioception after ACL injury

Stabilisation of the knee joint requires proprioceptive feedback in order for the muscles to react appropriately.[8] The afferent and efferent signals of the receptors in the ACL are carried by branches of the posterior tibial nerve.[8] It has been hypothesised that ACL rupture leads to changes in afferent inflow of the constituent receptors which causes a decrease in mechanical output due to deficits in motor unit activation and synchronous function.[164] Following rupture of the ACL there is thus believed to be a loss of both mechanical stability and proprioceptive acuity.[26, 157] Proprioception is most commonly assessed using tests of either joint position sense (JPS) or the ability to detect the onset of passive motion. Two meta-analyses compared proprioception between ACL-injured and asymptomatic knees based on such tests.[165, 166] One of the meta-analyses included only six studies but found significantly poorer knee proprioception for ACL-injured knees compared to the asymptomatic contralateral knees of the same individuals, as well as to those of controls.[165] Additionally, ACL-reconstructed knees showed significantly better knee proprioception compared to ACL-injured knees that had not been surgically reconstructed. In general, differences were most evident for tests of knee JPS rather than tests to detect the onset of motion. The second meta-analysis included sixteen studies which compared ACL-injured knees only to the contralateral asymptomatic knees. The results also showed significantly poorer proprioception for ACL-injured knees with greater deficits again evident for tests of JPS rather than motion.[166] However, the absolute differences in knee angles found in both meta-analyses were < 1° and thus the clinical significance of the findings was questioned. In fact a systematic review which included 11 studies did not find evidence for deficits in knee proprioception following ACL injury compared to controls.[167] Thus, given small absolute differences and the contradictory findings, it remains unclear as to whether clinically significant knee proprioception deficits exist following ACL injury and, if so, whether existing tests are capable of capturing them. Furthermore, one of many important considerations when interpreting these results is the different methods used to assess proprioception. According to the findings of the two meta-analyses mentioned here, tests of knee JPS appear to result in the greatest differences between ACL-injured and asymptomatic knees.

Knee JPS testing methods

Knee joint position sense tests usually involve the reproduction or matching of joint angles of the same or opposing limb, respectively.[168] However, many components should be considered when designing a knee JPS test. Firstly, the test procedure can be passive, active or visually estimated on an external device. Passive methods usually require a device such as an isokinetic dynamometer to provide a constant knee angular velocity. Active procedures are more versatile in that respect, but are harder to standardise due to variation in either knee angular velocity or force. However, active procedures are likely to have better ecological validity by more closely representing everyday activities.[169] Procedures of visual estimation often involve using goniometers or dummy joints to indicate joint angles and are less common. The angles used for starting position and the target angle itself may also be of importance. For example, it has been suggested that joint receptors are limit detectors and as such are more likely to play a role in JPS tests at the more extreme range of motion, whereas receptors in the muscles are more likely to dominate throughout the mid-range.[29] The starting and target angles will also determine both the range of motion over which the movement will take place and the direction in which the movement occurs, i.e. flexion or extension. Thus, for active movements in particular, the involved muscles will differ depending on this component. Isokinetic dynamometers are often utilised to maintain specific knee angular velocities and to provide knee angles with participants in a seated position. Standing knee JPS tests have however been encouraged to more closely resemble sporting activities and most often imply a weight-bearing procedure, thus incorporating resistance.[169] Other options for recording knee angles include motion capture systems and customised pulley devices. The accuracy of such equipment is an important consideration considering the small absolute differences in knee angle of < 1° found between ACL-injured knees and asymptomatic knees in previous meta-analyses.[165, 166] Partly due to these many modifiable factors, there remains no gold standard knee JPS test and methodological descriptions often fail to report all of these components sufficiently. It is thus not surprising that a systematic review of knee joint position sense tests found variable reliability across different methods among symptomatic and asymptomatic individuals.[170] Even if designing a reliable test, it has been suggested that simple biomechanical measures such as JPS errors may not sufficiently in detect adaptations in the complex sensorimotor system.[171]

Neuroplasticity after ACL injury

Plasticity as an attribute of the brain has been described as "the ability to make adaptive changes related to the structure and function of the nervous system" and can occur as a consequence of anatomical changes.[172] In 2006, Kapreli and Athanasopoulos[173] outlined a hypothesis of brain plasticity following injury of the ACL. They stated that the mechanoreceptors of the ACL under normal conditions provide afferent feedback to the CNS which is processed at three levels: 1) spinal cord, 2) brain stem, 3) motor cortex. Thus, injury to the ACL and subsequent damage to and/or loss of mechanoreceptors should cause a disturbance to the functional organisation of the CNS. Additionally, the related inflammation process was suggested as causing deafferentation of the end-plate and activation of receptors, which would otherwise have been inactive by altering their threshold levels. Adaptations in the brain should thus be evident from functional brain imaging analyses during movements at the knee. Subsequently, the same authors with additional colleagues performed an fMRI study of brain response to a single-joint knee extension/flexion movement among ACLD individuals classed as non-copers on average 26 months after injury and controls.[174] The results showed significantly less response for the ACL group in sensorimotor cortical areas and significantly greater response in the presupplementary motor area, posterior secondary somatosensory area and the posterior inferior temporal gyrus, which is located in the visual cortex. The authors speculated that ACL-deficient individuals may have thus relied more upon visualisation of the movements due to reduced proprioceptive feedback. Grooms et al.[175] performed a similar fMRI study among individuals on average 38 months after ACL reconstruction who had returned to activity and controls. Their results showed less response for the ACLR group in the ipsilateral motor cortex and cerebellum but greater response in several areas including the lingual gyrus, an area that has been associated with, e.g. limb positioning[176, 177] and movement perception.[177-179] The authors recommended incorporating multi-joint movements with joint position matching tasks to enhance the clinical applicability of future studies. A more recent study thus incorporated a hip and knee movement during fMRI and found increased activity for ACL-reconstructed individuals for regions associated with visual-spatial recognition and attention.[180] Thus, these studies in particular support the hypothesis of Kapreli and Athanasopoulos regarding brain plasticity post-ACL injury and several articles have since appeared in the literature to support and elaborate on this.[36, 181-183] From a clinical perspective, it is believed that the alterations in afferent stimuli may cause neuroplasticity that contributes to poor knee position sense and subsequent coordination errors which put the joint in positions of heightened injury risk even following current rehabilitation interventions.

Rationale for this thesis

ACL injuries can have devastating short- and long-term effects on individuals, including prematurely ending a sporting career and causing early onset knee osteoarthritis. Despite vast amounts of research over the previous decades, incidence rates for primary and secondary ACL injuries remain high. The resulting health care relating to physiotherapy and potential surgical intervention(s) are thus also burdens on society due to their associated financial costs. Modern training interventions, which often incorporate exercises to improve sensorimotor control and proprioception, do however appear to reduce ACL injury risk and associated negative outcomes. Identifying related deficits could thus help to better target interventions to those who would most benefit. This could help to reduce both primary and secondary injury risk, as well as improve quality of life in the long term. Currently, assessing knee function and proprioception does not seem to be standardised. Tests used for assessment also often lack evidence for their reliability, validity and responsiveness. Developing effective relevant tests and providing evidence for their implementation remains a goal for research. Additionally, growing evidence indicates neuroplasticity post-ACL injury. A better understanding of changes to the CNS could aid in the development of more advanced training interventions that further help to reduce negative outcomes to the injury and provide. Thus, more complex paradigms that incorporate tasks of lower limb proprioception are required to better understand the specific effects of ACL injury on brain response in areas associated with sensorimotor tasks.

Aims

The general aim of this thesis was to develop and assess tests of knee function, proprioception and related brain activity following injury to the ACL. The One-leg rise test was used to assess knee function, a systematic review and meta-analysis corroborated the evidence for existing knee JPS tests and three novel JPS tests were developed and applied as measures of proprioceptive acuity at the knee, one of which was implemented to investigate simultaneous brain response.

Specific aims were:

A. To establish knee function in the very long term after ACL injury based on performance and knee kinematic outcome variables of a One-leg rise (OLR) test among ACL-injured individuals treated with and without surgery, each compared to asymptomatic matched controls. (Paper I)

B. To assess the suitability of the OLR test as a reliable assessment tool of knee movement control in the very long term after ACL injury by determining the within-session reliability of the knee kinematics. (Paper I)

C. To structure a systematic research plan for the assimilation of evidence relating to the psychometric properties of knee proprioception tests among individuals with ACL injury and asymptomatic persons. (Paper II)

D. To assimilate the evidence for the psychometric properties of existing knee JPS tests among individuals with ACL injury by performing a systematic review and meta-analysis of the literature. (Paper II and III)

E. To develop reliable knee JPS tests suitable in the early stages of rehabilitation from ACL injury, during fMRI and after RTS. Also, assess the discriminative validity of the novel knee JPS tests and potential role of activity level on outcomes by comparing ACL-injured individuals to activity-matched athletes and less-active controls among asymptomatic controls. (Paper IV)

F. To investigate which brain regions are recruited when performing a knee JPS test and whether response correlates with JPS errors by incorporating lower limb kinematics with simultaneous fMRI among ACL-reconstructed and asymptomatic individuals. (Paper V)

G. To compare brain response and errors during a knee JPS test between individuals with ACL reconstruction and matched asymptomatic controls. (Paper V)

Materials and Methods

Design and overview of the papers

This thesis consists of five papers based on four different data collections. Experimental data collections for Paper I, IV and V were performed at the U-Motion laboratory at the Department of Community Medicine and Rehabilitation, Umeå University, Sweden. Paper V also included additional data collection at the Umeå center for Functional Brain Imaging (UFBI). Paper I was based on a long-term follow-up which included individuals with ACL injury treated either with or without surgical reconstruction as well as asymptomatic persons, all aged 35-63 years. Paper IV and V were two separate data collections which included individuals aged 17-34 years with ACL reconstruction and asymptomatic persons, as well as elite athletes for Paper IV. Paper II is the accompanying protocol to Paper III, which is a systematic review and meta-analysis for which data was retrieved online from existing studies.

- Paper I: a cross-sectional study including three groups: 1) 33 ACL-reconstructed individuals (ACLR), 2) 37 ACL-injured individuals treated with physiotherapy only (ACLD) and 3) 33 age- and sex-matched asymptomatic controls (CTRL). For ACL-injured participants, rupture had occurred on average 23 (17-28) years previously. Participants performed the One-leg rise test on one occasion.
- Paper II: a protocol which describes the background and proposed methods of a systematic review and meta-analysis investigating the psychometric properties of all existing knee proprioception tests that have been applied among asymptomatic individuals and those with ACL injury.
- Paper III: a systematic review including 80 studies and meta-analyses of the psychometric properties (reliability, validity and responsiveness) of knee JPS tests targeting individuals with ACL injury.
- Paper IV: a reliability (test-retest) and cross-sectional study. For reliability, 24 asymptomatic individuals performed two knee JPS tests on two separate occasions on average 16.3 ± 6.7 days apart. For discriminative (known-groups) validity, both tests were performed once by the following three groups: 1) 18 ACL-reconstructed individuals (reconstruction performed on average 23 ± 16.4 months prior), 2) 23 asymptomatic controls and 3) 21 elite athletes.
- Paper V: a cross-sectional study including three groups: 1) 10 individuals with right-side ACL reconstruction (R-ACLR), 2) 11 individuals with left-side ACL reconstruction (L-ACLR), and 3) 19 age-, sex-, height-, mass-, and activity level-matched asymptomatic controls. Participants performed a supine knee JPS test during simultaneous functional magnetic resonance imaging (fMRI).

Participants

Paper I

ACL-injured participants were recruited from two hospitals in the north of Sweden. Eligibility criteria required: unilateral ACL injury, no hip or knee replacement surgery, and no inflammatory/rheumatic disease or neurological pathology. Of an initial 113 individuals, 81 were considered eligible. Eleven individuals declined to participate in the study and thus 70 ACL-injured participants were included. ACL injuries occurred on average 23 (17-28) years prior to testing. These individuals were from two different cohorts who received different treatment: 1) 33 individuals who had received ACL-reconstruction using a patellar tendon autograft (ACLR); 2) 37 individuals with ACL injury who had been treated with physiotherapy only (ACLD). An age- and sex-matched control group (CTRL) with asymptomatic knees were recruited via convenience sampling.

Paper IV

Participants were recruited via advertisements, sports clubs, word of mouth and, additionally for ACL-injured participants, via local orthopaedic clinics. Eligibility criteria required: 17-35 years of age, no disease or injury that could affect knee proprioception other than ACL injury and possible concomitant meniscus injury for the ACL group. For test-retest reliability, 24 individuals with asymptomatic knees were eligible for the study and agreed to participate. For discriminative analyses, three groups were recruited: 1) 18 individuals aged 23 ± 4.4 years who had received ACL reconstruction using a hamstring autograft 23 ± 16.4 years prior to testing and had been cleared for RTS (ACLR); 2) 23 less-active individuals aged 23.5 ± 3.4 years with asymptomatic knees (CTRL); 3) 21 elite athletes aged 21.2 ± 2.9 years with asymptomatic knees who performed regular knee-specific training (ATHL).

Paper V

Participants were recruited via advertisements, word of mouth and, for ACL-injured participants, also via local orthopaedic clinics. Eligibility criteria required: Tegner activity score of at least 4 (equivalent to recreational sports such as cycling or jogging twice a week), no injuries or diseases (other than ACL injury and possible concomitant meniscus injury for ACL-injured participants) that could affect the CNS or proprioception of the lower limbs. ACL-injured participants were additionally required to have unilateral ACL reconstruction with hamstring autograft and clearance for full RTS. For test-retest reliability, 15 asymptomatic individuals were included. Due to brain imaging analyses potentially being confounded by mixing right- and left-side ACL injuries in the same group, participants were divided into three groups: 1) 10 individuals aged 24.8 ± 4.2 years with right-side ACL reconstruction performed 19.5 ± 10.0 months previously (R-ACLR); 2) 11 individuals aged 28.2 ± 4.7 years with left-side ACL reconstruction performed 28.2 ± 18.7 months prior to testing (L-ACLR); 3) 19 asymptomatic controls aged 27.1 ± 4.6 years (CTRL). All three groups were matched for sex distribution, age, body height, body mass and current activity level (Tegner). Overviews of the group data for all participants included in validity and reliability analyses in the primary research papers of this thesis (Paper I, IV and V) are provided in Table 1 and Table 2, respectively.

Ethics

Ethical approval was obtained from the Regional Ethical Review Board in Umea for the primary research papers I (Dnr. 08-211M), IV and V (both Dnr. 2015/67-31). Paper II and III did not require ethical approval. The participants of the primary studies provided their written informed consent prior to testing in accordance with the declaration of Helsinki. Risks for participation were deemed minimal and measures were taken to minimise these as much as possible. For Paper I and IV, test batteries were performed which included maximal physical tests including hops and voluntary muscular contractions. To minimise the risks associated with such exertions, screening of potential participants during recruitment ensured that all individuals were comfortable performing such tasks and had experience of doing so. Additionally, an aerobic warm up on an exercise bike lasting six minutes was performed at the start of the session for Paper I and a gradual succession of increased difficulty served as a warm up for the test battery related to Paper IV. A standardised number of practice attempts for each test were also performed. The supine knee JPS tests of Paper IV and V were not considered to be strenuous or to cause discomfort. However, the WB JPS test of Paper IV involved single-leg squats which required sufficient muscular strength and range of motion of the lower extremity joints. Thus, prior to testing, the ability of the participants to perform the test at the greatest range of motion was assured before commencing. For Paper V, risks from lying in an MRI scanner are relevant for individuals who may be pregnant or have metal objects in their bodies. Also, claustrophobia can be experienced by some individuals due to the enclosed environment. Careful screening of participants during recruitment ensured suitability for MRI participation and doctor referrals were obtained. A minimum of one researcher qualified in first aid was present throughout all data collections and appropriate equipment was available. However, no incidents occurred and thus medical attention was not required. However, one participant experienced feelings of claustrophobia in the MRI scanner and chose to cease participation during the test. The individual had not expected to experience such issues and no lasting effects were apparent once no longer lying in the scanner.

Table 1. Background data for the groups included in validity analyses for Paper I, IV and V presented in means (standard deviation), except for total (n) where stated and median (range) for questionnaires.

	Paper I			Paper IV			Paper V		
	ACLR	ACLD	CTRL	ACLR	CTRL	ATHL	R-ACLR	L-ACLR	CTRL
Participants, n	33	37	33	18	23	21	10	11	19
Males:females, n	21:12	23:14	21:12	3:15	3:20	3:18	4:6	4:7	7:12
Age at test, years	45.6 (4.5)	48.1 (5.9)	46.7 (5.0)	23.0 (4.4)	23.5 (3.4)	21.2 (2.9)	24.8 (4.2)	28.2 (4.7)	27.1 (4.6)
Height, m	1.74 (0.09)	1.74 (0.08)	1.76 (0.10)	1.70 (0.06)	1.70 (0.07)	1.71 (0.08)	1.72 (0.09)	1.73 (0.09)	1.75 (0.08)
Body mass, kg	83.0 (15.6)	87.1 (14.9)	77.4 (14.9)	67.5 (10.2)	64.4 (7.1)	65.7 (9.1)	72.6 (7.8)	72.1 (11.0)	73.1 (9.9)
BMI, kg/m^2	27.2 (3.3)	28.9 (4.6)	24.6 (2.5)	23.2 (2.7)	22.4 (2.2)	22.3 (2.0)	24.6 (1.6)	24.0 (1.6)	23.8 (2.2)
Years since injury	23.9 (2.8)	23.1 (1.3)	-	-	-	-	-	-	-
Years since surgery	20.1 (1.5)	-	-	1.9 (1.4)	-	-	1.7 (0.8)	2.4 (1.5)	-
Questionnaires									
Tegner at test	4.0 (4.0)	4.0 (5.0)	6.0 (4.0)	7.0 (5.0)	4.0 (5.0)	8.0 (1.0)	5.5 (5.0)	7.0 (5.0)	6.0 (5.0)
Tegner pre-injury	9.0 (7.0)	9.0 (6.0)	-	9.0 (3.0)	-	-	8.5 (3.0)	8.0 (7.0)	-
IKDC 2000, %	-	-	-	83.4 (35.6)	100 (9.2)	100 (33.3)[a]	77.6 (14.1)	77.0 (15.0)	-
Lysholm score	81.0 (64.0)	71.0 (64.0)	100 (0.0)	88.5 (36.0)	100 (10.0)	100 (15.0)[a]	86.0 (12.5)	86.0 (5.0)	-
TSK score	32.5 (33.0)[a]	32.0 (29.0)	-	30.0 (24.0)	-	-	36.5 (11.5)	33.0 (5.0)	-
Marx activity score	-	-	-	-	-	-	12.0 (6.5)	10.0 (7.0)	11.0 (7.0)

[a]Data missing from one participant.

ACLD, anterior cruciate ligament-injured individuals treated with physiotherapy only; ACLR, anterior cruciate ligament-reconstructed individuals; IKDC, International Knee Documentation Committee Subjective Knee Form; L-ACLR, left-side ACLR individuals; R-ACLR, right-side ACLR individuals; TSK, Tampa Scale of Kinesiophobia.

Table 2. Background data for the asymptomatic groups included in reliability analyses for Paper IV and V presented in means (standard deviation) unless totals (n).

	Paper IV	Paper V
Participants, n	24	15
Males:females, n	2:22	9:6
Age at test, years	22.5 (3.3)	25.0 (3.1)
Body height, cm	1.69 (0.07)	1.78 (0.09)
Body mass, kg	63.2 (8.5)	74.4 (11.2)
BMI, kg/m^2	22.2 (2.4)	23.5 (2.2)

Test procedures

For all primary research papers (I, IV and V), participants began by completing relevant questionnaires covering aspects such as knee function, fear of movement and activity level, as described previously.[184, 185] The questionnaires included in the papers of this thesis are detailed below under *Self-administered questionnaires* and the results are reported in Table 1. Also, hand and leg dominance was ascertained based on answers to the questions "Which hand do you prefer to write with?" and "Which foot do you prefer to kick a ball with?" (prior to injury for ACL groups), respectively. Body height and mass were measured using a wall-mounted stadiometer and calibrated weighing scales, respectively. For Paper I and IV a qualified physiotherapist performed a clinical examination immediately prior to the commencement of testing. For Paper I, electromyography (EMG) equipment and a motion capture maker set were then affixed to the participants. For Paper IV, an initial marker set was affixed to participants for performance of the knee JPS tests before the remaining markers and EMG equipment were applied for the remaining test battery. The EMG data were not included in the papers of this thesis. For Paper V, the marker set was applied first in the U-Motion laboratory for the familiarisation session and then re-applied immediately prior to testing in the MRI scanner. Descriptions of the marker sets are provided in the *Motion capture* section under *Data collection* and are also detailed and illustrated in the appendix.

Self-administered questionnaires

A number of commonly-used self-administered questionnaires were completed by participants in the papers of this thesis to provide patient-reported outcomes related to activity level, knee function and fear of movement. The questionnaires facilitated comparisons between groups within the same studies as well as between external studies and those of this thesis. Each questionnaire is detailed henceforth.

Tegner activity grading scale

The Tegner activity grading scale was first proposed by Tegner and Lysholm[186] in 1985. The scale was designed as a complement to functional scores in the evaluation of knee ligament injuries. Grades range from 0 (e.g. sick leave because of knee problems) to 10 (e.g. elite football [soccer] player). The scale covers work-related activities, recreational activities and sports, as well as competitive sports. Activities and sports that place greater demands on the knee joint, i.e. that involve sudden changes of direction and landings, are reflected in higher scores. Thus, the higher the grade, the greater likelihood that the individual has good knee function. For individuals with knee ligament injuries, it is common to report pre-injury grade, current grade and at which grade they would like to be. The use of this scale has become so common that the original article is the most cited within the area of ACL injury.[187] The Tegner activity grading scale was administered in all primary research papers of this thesis to provide an indication of activity level and thus self-reported knee function of all participants.

International Knee Documentation Committee Subjective Knee Form 2000

A questionnaire developed by a committee of international knee experts published in 2001.[188] The original publication found it to be a reliable and valid measure of knee-related symptoms, sports activities, function and daily living among individuals with a range of knee problems. Scores range from 0-87 with the overall results presented as a percentage. Higher scores indicate favourable results. It was administered in Paper IV and V of this thesis.

Lysholm knee scoring scale

The Lysholm knee scoring scale was published by Lysholm and Gillquist in 1982.[189] It is a questionnaire designed as a follow-up to knee ligament surgery with an emphasis on symptoms of knee instability. Consisting of eight questions, an overall score of 0-100 is possible, with higher scores indicating better knee function in everyday situations. The original publication is the second most cited within ACL research.[187] It was used in all primary papers of this thesis to provide an indication of knee function.

Tampa Scale for Kinesiophobia

The Tampa Scale for Kinesiophobia was first presented by Miller, Kori and Todd in 1991.[190] It consists of 17 questions each rated 1-4 and thus overall scores range from 17-68, with higher scores indicating a greater fear of movement. The Swedish version was developed and published in 2004 by Lundberg, Styf and Carlsson,[191] who found it to be a reliable and valid tool to assess fear of movement among individuals with chronic low back pain. It is a commonly applied questionnaire among individuals with ACL injury, for whom scores have been associated with knee-related quality of life.[192] It was administered among all individuals with ACL injury in each primary research paper of this thesis.

Marx activity scale

A rating scale of activity level published by Marx and colleagues in 2001 who demonstrated its reliability and validity.[193] It was intended to take little time to complete (< 1 minute) and to be relevant across different sporting activities. It consists of four questions related specifically to the frequency that movements associated with sports, e.g. a change of direction during running, are performed. Each question is rated 1-5 and thus overall scores range from 4-20, with higher scores indicating a greater activity level. The Marx activity scale was administered among all participants of Paper V.

One-leg rise test protocol

For Paper I, the OLR was performed as one of nine tests in a test battery (for more details regarding the other tests, see Tengman[185]). The OLR was based on the test previously reported by Thorstensson and colleagues[194] to assess functional performance of the lower extremity among individuals with chronic knee pain. The test involves repetitive standing and sitting from a stool on one leg. Thus, participants began by sitting on a stool 0.48 m in height with only the foot of the tested leg in contact with the floor in front of them. The fixed stool height for all participants was intended to improve ecological validity of the test compared with standardising the height based on body height or lowering with successive repetitions as has been done in other studies.[195, 196] Arms were crossed over the chest throughout for standardisation purposes. All ACL-injured participants performed first with their non-injured leg and controls with their dominant leg. Following one practice repetition, consecutive sit-stand-sit movements were performed at a self-controlled pace encouraged to ensure control of movement throughout the entirety of the movement, e.g. sitting from the standing position was to be performed under control rather than falling back on to the stool. After a minimum two-minute rest, the test was repeated with the contralateral leg. In instances when participants performed 50 repetitions, testing was ceased in accordance with a previous protocol.[197] The maximum of 50 repetitions was however not known to participants prior to testing. Upon failure of one repetition, testing was ceased. Failure was defined if the contralateral foot contacted the floor or weight-bearing leg, or if the foot of the weight-bearing leg moved position.

Novel knee JPS test protocols

For Paper IV, two novel active knee JPS tests were developed: 1) a supine NWB test, and 2) a standing WB test. The NWB test was designed with two applications in mind. Firstly, identifying individuals with poor proprioceptive acuity in the early stages of rehabilitation may be advantageous in facilitating targeted training. Common tests of knee JPS test are usually performed using an isokinetic dynamometer, which is often not available in clinics. Also, WB tests are often not appropriate during the early stages of rehabilitation due to pain, swelling and reduced range of motion. A heel slide exercise is however commonly used in the early stages of rehabilitation. A towel or similar item is often placed under the foot on a hard floor to allow smooth flexion/extension movements. Thus, such a set up was deemed to be suitable even in the early stages of rehabilitation after ACL injury. The second application regards brain imaging. When designing our test, a similar set up involving both the hip and knee had been applied in an MRI scanner to assess the effects of knee bracing on brain response.[198] However, no proprioceptive task was involved in that particular study. Additionally, both the Kapreli[174] and Grooms[175] studies involving ACL-injured participants incorporated paradigms including supine tasks of lower limb movement, but were restricted only to the knee. Grooms recommended tasks involving multi-joint movements as well as the incorporation of tests such as position matching.[175] Thus, a supine NWB test incorporating movements of the entire lower limb was considered suitable for the majority of ACL-injured participants and for application in an MRI environment. The WB test was designed to provide a more functional test of JPS. As mentioned previously, such tests have been encouraged to better mimic real-life situations, yet few appear in the literature. This is of particular relevance for RTS decision-making and for assessment post-RTS. Table 3 provides an overview of the novel knee JPS tests included in this thesis and detailed descriptions of each test protocol are provided thereafter.

Table 3. An overview of the components of the active knee joint position sense tests included in Paper IV and V of this thesis.

	NWB test	WB test	fMRI test
Paper of thesis	IV	IV	V
Environment	Laboratory	Laboratory	MRI scanner
Measurement equipment	MoCap	MoCap	MoCap
Body position	Supine	Standing	Supine
Test procedure	Active - Active	Active - Active	Active - Active
First leg to perform	NI/Dominant	NI/Dominant	Randomised
Consecutive trials per leg	10	2	Randomised
Type of instructions	Visual	Audio	Visual
Movement direction	Extension	Flexion	Flexion
Knee angular velocity	~10°/s	~10°/s	~10°/s
Starting angle	~100°	~0°	~0°
Target angle cue	40° and 65°	40° and 65°	35° and 60°
Target angle order	40°, 65° alt.	40°, 65° alt.	Randomised
Memorisation time	~2 secs	~2 secs	~8 secs
Events defined	Trigger	Trigger	Kinematics
Outcome measure	CE, AE, VE	CE, AE, VE	AE

AE, absolute error; alt., alternating; CE, constant error, fMRI, functional magnetic resonance imaging; MoCap, motion capture (three-dimensional); NWB, non-weight-bearing; VE, variable error; WB, weight-bearing.

Non-weight-bearing knee JPS test

For the NWB test, participants lay supine on an exercise mat placed on the floor in the U-Motion laboratory (see Figure 2). Their feet and shanks were strapped in by hook-and-loop fasteners to foot holders of a custom-built device which allowed extension and flexion movements of the hip and knee. This device was used for both novel supine tests of this thesis. Non-stick Teflon sheets were affixed under each foot on the underside of square wooden boards which moved on top of plastic strips affixed to the device. Knee flexion was restricted to 100°, which was the approximate start position for this test. One leg was tested at a time while the resting leg remained in flexion with the foot externally rotated in a stop block to avoid active holding. Once in position, participants performed two full extension and flexion movements for each leg. The markers were tracked in Qualisys Track Manager software and a model was created which facilitated real-time registration of knee kinematics. A wooden box with in-built mirror was then placed on the floor covering the head of the participant. The mirror was angled to reflect a display screen approximately three metres behind the participant. A piece of black cloth attached to the box occluded vision of their legs. Participants performed three extension/flexion movements with one leg at an attempted knee angular velocity of 10°/s during extension with the help of real-time feedback in the form of a graph. This angular velocity was chosen in line with previous studies.[199-205] Knee angular velocity during flexion, i.e. returning to the start position, was requested to be moderate. ACL-reconstructed participants started with their non-injured leg and asymptomatic participants with their dominant leg. The test started with instructions to flex the leg until a stop sign appeared. Once stopped, instructions encouraged memorisation of the knee angle and three seconds later prompted a return to the start position. Three seconds after returning to the start position, participants attempted to reproduce the previous knee angle and then returned once again to the start positon. This procedure was then repeated after approximately one minute of rest with the contralateral leg.

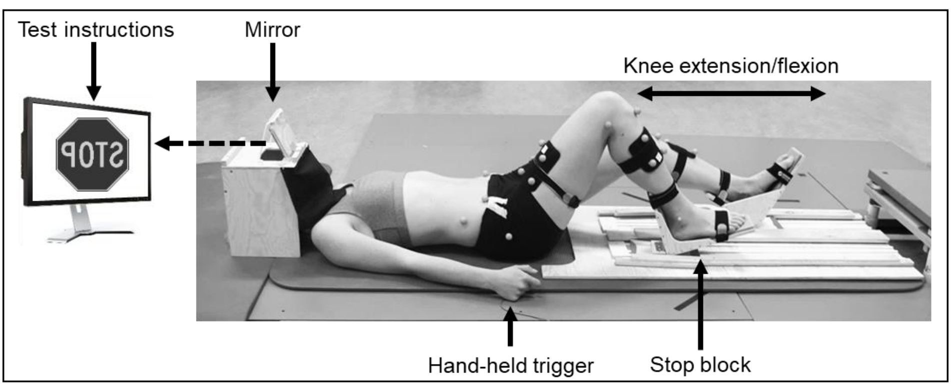


Figure 2. An illustration of a participant performing the non-weight-bearing knee JPS test from Paper IV of this thesis with their left leg.

Weight-bearing knee JPS test

For the WB test, participants stood on a 0.36 m raised platform with a solid 8° wedge underneath the WB foot to reduce tension in the triceps surae in line with a previous study[206] (see Figure 3). A vertical steel pole was affixed between the floor and ceiling anteriorly and centrally to the platform at an individualised distance which participants were able to hold in order to aid balance. The position of the pole was intended to provide a 90° elbow angle with the upper arm at their side. Participants were encouraged to maintain this angle throughout the test to avoid upper extremity positional feedback had the hand remained in the same place. To aid smooth vertical movement, a cloth was loosely wrapped around the steel pole. Firstly, with participants standing in the centre of the platform, two knee lifts to approximately 90° hip flexion per leg were performed and recorded using the motion capture system. These marker trajectories were subsequently tracked and a new AIM was created. Standing on one edge of the platform with the resting leg hanging, participants used similar graphical feedback to the NWB test to practice a knee angular velocity of 10°/s during three one-leg squat movements per leg. To check the maximum knee range of motion for the ACL-reconstructed participants, a one-leg squat was performed on the platform to the greatest knee angle possible before causing discomfort. This angle was noted by the test leader and the maximum angle for the test could be adjusted. For the participants of this paper, no angles needed to be adjusted. Participants then took a hand-held trigger button in the ipsilateral hand of the leg to be tested and put on a blindfold. When ready, participants were asked by the test leader to squat until they heard a loud beep sound. Upon hearing the beep, participants held the angle and pressed the trigger button to confirm the TA. Three seconds after the first beep, a second beep indicated that they should return to the starting position. The test leader then verbally instructed the participants to reproduce the previous knee angle, press the trigger button once stopped and then immediately return to the start position. To avoid potential effects of fatigue, only two consecutive repetitions were performed on each leg. Participants were thus required to cross over to the other side of the platform following each second repetition. For both tests, all instructions were activated based on either the knee angle or knee angular velocity, thus provided instructions at the appropriate time for each individual. Also, the respective stop cue was activated once the knee angle reached 40° for the first repetition and then alternated with 65° for the remainder of the test. The range of 40°-80° has previously been shown to be reliable for knee JPS tests.[207] Participants were however under the impression that knee angles were entirely random. If knee angular velocity deviated by more than 5°/s for consecutive repetitions, participants were orally reminded by the test leader to adjust accordingly.

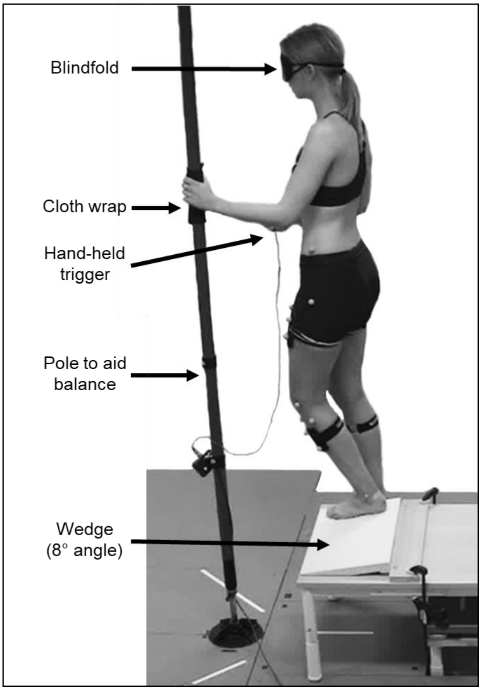


Figure 3. An illustration of a participant performing the weight-bearing knee JPS test from Paper IV of this thesis with their left leg.

Knee JPS test for brain imaging

For Paper V, an adapted version of the supine NWB test of Paper IV was developed for improved suitability during simultaneous brain imaging in the MRI scanner (see Figure 4). Firstly, a shortened version of the protocol was performed in the U-Motion laboratory for familiarisation purposes. The same custom-made extension/flexion board was used with wooden box and in-built mirror. However, the start position was with legs in full extension. Also, the stop sign was activated at 35° and 60° flexion. This was changed because during the previous NWB knee JPS test, target knee angles were overshot by approximately 5° due to a combination of system delay and participant reaction time. Thus, activation of the stop sign at these angles was intended to result in actual TAs of approximately 40° and 65° respectively. Another difference was the randomisation of angles and legs. This was more appropriate for this test as the full extension start position did not require the participants to externally rotate the foot in order to rest the respective leg. Further, memorisation times were extended for the familiarisation session to five seconds. Knee angular velocity was similarly practiced three times on each leg and was encouraged both during flexion and extension. Five repetitions were performed per angle condition for each leg. An extended version of this protocol was then performed after approximately 30 minutes during simultaneous brain imaging in the MRI scanner. For the MRI protocol, participants lay in the scanner with their feet and shanks affixed in the same custom-built extension/flexion device. Ear plugs were used to reduce noise from the scanner. Headphones and an in-built microphone were used in order to allow communication with the test leader and staff of the MRI scanner. JPS test instructions were presented on a computer screen, which were seen via a tilted mirror attached to the head coil. To reduce head movements, a strap was tightened over the torso of the participants. Also, soft cushions were placed inside the head coil to provide stability. The protocol for the MRI scanner was similar to that during the familiarisation session. However, in the MRI scanner, memorisation time was extended further to eight seconds. Also, the number of repetitions was increased for each angle and leg to eight. Two further conditions, one active and one resting, were added to the MRI protocol for brain imaging analyses purposes. The added active condition involved flexion and extension without a JPS task and was performed eight times per leg and randomised time points throughout the protocol. The resting condition was an extended time of 15 seconds in the start position and was performed five times at evenly distributed time points throughout the protocol. The total length of the protocol was estimated at approximately 38 minutes based on a constant knee angular velocity of 10°/s. Due to the requirements of providing an exact total scanning time prior to testing, scanning time was thus set at 40 minutes to allow for potentially slower performance.

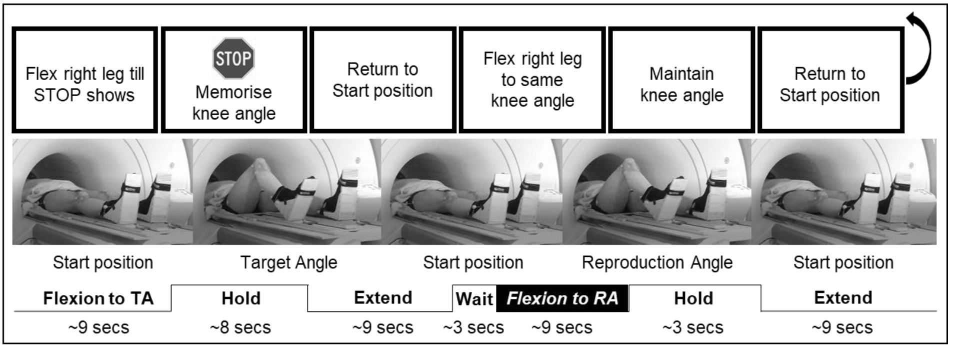


Figure 4. An illustration of an individual performing one repetition of the knee JPS test from Paper V of this thesis with their right leg in the MRI scanner. The instructions towards the top were displayed on a screen at the back of the scanner and were visible to the participant via an in-built mirror at the top of the head coil. Brain imaging data relating to response to the knee JPS test were extracted during the highlighted block “Flexion to RA”. RA, reproduction angle; TA, target angle.

Data collection

The test leader remained the same for the entire data collection within each primary research paper (I, IV and V), but test leaders differed between each paper. The respective test leaders were thus responsible for applying the markers for motion capture and EMG equipment, as well as providing standardised instructions throughout.

Motion capture

An eight-camera three-dimensional motion capture system (Oqus 300, Qualisys AB, Gothenburg, Sweden, 240 Hz) was used in the U-Motion laboratory for Paper I and IV, as well as for the familiarisation session for Paper V. Also for Paper V, a three-camera motion capture system (Oqus MRI Qualisys AB, Gothenburg, Sweden, 120 Hz) was used in the MRI environment. This system is specially designed for MRI environments by the use of non-magnetic materials and shielding to reduce electromagnetic emissions which could otherwise cause artefacts in imaging data. For Paper I, a two-dimensional video camera was positioned approximately three metres in front and slightly to the side of participants to provide a diagonal view of movements for post-testing control of performance. For Paper I, 42 retro-reflective passive spherical markers were used in the marker set. The markers were affixed with double-sided adhesive tape to the skin at specific anatomical landmarks of the trunk and lower body. This was an adapted version of a Helena Hayes marker set and has been described in detail previously.[139] Details are also provided in the appendix of this thesis.

For each knee JPS test (Paper IV and V), knee angles were recorded with motion capture in the sagittal plane based on the markers in line with the greater trochanter, lateral femoral epicondyle and the lateral malleolus. The remaining markers provided extra stability to the real-time models but did not contribute to outcomes. For Paper V, markers for the greater trochanters and lateral malleoli were placed on sticks (wand markers) 56 mm and 46 mm in length, respectively, to improve visibility for the cameras in the MRI room. Three-dimensional motion capture requires that each marker is visible by at least two cameras. Thus, with three cameras in the MRI room, the centrally-placed camera was required to capture all markers, the majority of which were placed laterally on participants. The extra length provided by the wand markers thus ensured that they were in the field of vision for the central camera throughout the movements. The marker sets for each test are detailed and illustrated in the appendix. For the NWB and WB test of Paper IV, a trigger button held by the participants provided analogue events in the data to denote the target and reproduction angles. For the supine test of Paper V, no hand-held trigger was used in order to avoid an extra task during testing in the MRI scanner which would have confounded analyses of brain response. Knee angles were defined using kinematic data for this test.

Systematic review and meta-analysis

Data collection for Paper III was performed online by systematically searching scientific databases for research studies that implemented any form of knee proprioception test among either asymptomatic individuals or those with ACL injury. Search terms and strategies were adapted specifically to the individual databases in an attempt to identify as many relevant articles as possible and are detailed in Paper II. The following databases were searched: PubMed; Allied and Complementary Medicine (AMED via EBSCO); the Cumulative Index to Nursing and Allied Health Literature ([CINAHL] via EBSCO); SPORTDiscus (via EBSCO); Web of Science; Scopus; the Cochrane Central Register of Controlled Trials (CENTRAL); Physical Education Index (via ProQuest). Google Scholar was also searched using relevant terms. All retrieved articles were exported to EndNote (version X9.3.1, Clarivate Analytics Software, Philadelphia, USA) and then to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.). Two authors (AS, ET) screened titles and abstracts and subsequently the full texts of those articles considered to be potentially eligible for inclusion. Eligibility screening was performed systematically according to a questionnaire displayed in Paper II (Box 1). All articles deemed eligible after the full text stage were categorised based on the type of knee proprioception test, e.g. JPS or threshold to detect passive motion, and the study group, i.e. ACL-injured and/or asymptomatic individuals. For Paper III, only those studies that included at least one test of knee JPS and ACL-injured individuals were included. The remaining studies will be included in forthcoming systematic reviews. Disagreements between the two authors responsible for screening were resolved either by consensus or by consulting a third author (AA).

Data extraction was then performed for all included studies. For each study, one author was assigned as first reviewer and one other as second reviewer. The role of the first reviewer was to initially extract data regarding identification of any psychometric property (PMP) evaluated, study design, population demographics, test design, statistics and relevant results. The role of the second reviewer was to verify the data that had been extracted by the first reviewer. In instances when important information was missing, contact was attempted with at least one of the study authors either by sending an e-mail to the address provided in the published article or by searching for contact information online, e.g. on the website of the institution where the author(s) was registered or via ResearchGate.

Functional magnetic resonance imaging

For Paper V, fMRI data was collected using a 3T General Electric MRI scanner with a 32-channel head coil to quantify brain response based on the blood-oxygen-level-dependent (BOLD) signal. The BOLD signal is an indirect measure of neuronal activity based on the concentration of oxygen in the blood.[208-211] For a detailed description of the BOLD signal, the reader is directed to the review by Logothetis and Wandell.[211] Briefly, the magnetic properties of haemoglobin depend on its oxygenation.[209] Deoxyhemoglobin, in contrast to oxygenated haemoglobin, is paramagnetic and causes changes in the MR signal.[210, 212] Neural activation causes a decrease in oxygen followed by an increase of cerebral blood flow.[211] Importantly, there follows an overcompensation of oxygenated blood supply which results in an increase in the BOLD contrast.[211, 213] It is such fluctuations in MR signal that are used to make inferences regarding brain response. A gradient-echo-planar imaging sequence was used with the following scanning parameters: repetition time = 2000 msec, echo time = 30 msec, flip angle = 80°, field of view = 25 cm. Thirty-seven transaxial slices with a thickness of 3.4 mm (0.5 mm gap) were acquired. Ten initial dummy scans were collected for the fMRI signal to reach equilibrium and discarded prior to analysis.

Data processing

Kinematics

For the kinematics of Paper I, IV and V, marker trajectories of the recorded motion capture files were tracked using Qualisys Track Manager software (version 2.2, Qualisys AB, Gothenburg, Sweden). For Paper I, trajectories were gap-filled up to a maximum of 24 ms using polynomial interpolation when deemed appropriate. For Paper IV and V, marker trajectories for all knee JPS tests were tracked using the existing real-time models created for each testing session for each individual. Marker data were then extracted to Visual3D processing software (Visual3D Professional version 5.02.23, C-Motion Inc., Germantown, Maryland, USA). For Paper I, a low-pass filter was applied using a second-order Butterworth filter and cut-off frequency of 6 Hz. A five-segment rigid body model was then constructed which consisted of two shanks, two thighs and one pelvis. Joint centres were based on a 6-degrees-of-freedom model. The data was checked by the first author and no trajectories were gap-filled. For Paper IV, data were filtered at 15 Hz with a critically damped digital filter. For Paper V, data were filtered with a 6 Hz fourth-order low-pass zero-lag Butterworth filter. For Paper IV and V, kinematics were based on knee angle in the sagittal plane.

One-leg rise test

Performance data

The number of consecutive OLR repetitions for each leg was first noted by the test leader during testing and checked later using 2D video analysis by the first author of the paper. In instances of doubt as to whether a repetition should have been regarded as successful or a failure, the test leader and first author watched the video footage together and came to a consensus. However, a number of participants had issues with their balance during the first repetition, most often due to a non-optimal position of the weight-bearing foot, e.g. too far away from the stool. Thus, these participants were allowed a second attempt. An additional performance variable was the relative time taken to complete four phases, defined based on the vertical velocity of the hip joint centre: 1) *Rise* began when velocity exceeded 10% of its maximum, 2) *Stand* began when velocity was next below 10% of its maximum, 3) *Down* began when velocity was next below 10% of its minimum, and 4) *Sit* began when velocity next exceeded 10% of its minimum. We considered this an interesting and relevant analysis because we believed it to give an indication of the strategy and control during the test. For example, we hypothesised that those who found the task more difficult may have spent a longer time in the *Stand* and *Sit* phases in order to rest, as well as less time particularly during the *Down* phase due to a lack of eccentric muscular control. Total absolute time was also considered of interest with the hypothesis that those who found the task harder would take a longer time to complete their repetitions. These phases were thus presented as normalised time in percentages as well as total time in seconds.

Kinematic data

The kinematic variables of knee abduction and adduction maximum, as well as knee movement units, were subsequently extracted only for the *Rise* and *Down* phases. Knee abduction was chosen because evidence has indicated this to be greater among ACL-injured individuals than controls in similar one-leg half squats.[214, 215] Knee movement units was operationally defined for Paper I based on the mediolateral velocity profile of the knee joint. The number of velocity peaks were calculated, with a greater number assumed to indicate less knee stability. Similar measures have been applied previously, with ACL-injured individuals showing less knee stability[216] and less mediolateral control associated with poorer knee proprioception.[217] The knee joint angles were thus defined based on the rotation of the shank relative to the thigh using the Cardan X-Y-Z convention: X represented flexion/extension, Y represented adduction/abduction, and Z represented internal/external rotation.[218] The first repetition was omitted from kinematic analyses because participants most often began in a slightly different position, i.e. more upright, compared to subsequent repetitions. Also, despite participants performing up to 50 repetitions, it was deemed appropriate to assess the first ten included repetitions (repetitions 2-11) when available to avoid potential fatigue effects on kinematics while still providing sufficient data.

Risk of bias ratings and quality assessment of PMPs

Once data had been verified, the risk of bias (RoB) for each study was evaluated using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) RoB checklist.[219] The checklist includes different boxes which relate to specific PMPs. For each box, relevant questions must be answered by choosing the appropriate score. For example, for the box relating to reliability, the second question asks "Was the time interval appropriate?". The best score of "very good" is analogous with the answer "Time interval appropriate". However, the worst score of "inadequate" is analogous with the answer "Time interval NOT appropriate". The overall rating for each box is based on the worst score of the included questions. For example, if a study receives scores of very good for four questions in the same box but inadequate for one, then the overall rating for the RoB for that particular PMP of that study would be inadequate. For Paper III of this thesis, boxes 6-10d (reliability, measurement error, criterion validity, hypothesis testing for construct validity and responsiveness) were included. Each of these PMPs and their subdivisions are defined in Table 4. In an attempt to standardise ratings, two studies were initially assessed independently by all five authors and ratings were discussed during a meeting. The same authors who had performed data extraction for the particular studies also assessed RoB but independently of each other before being compared and agreed upon. All responsibilities were shared between the five authors, ensuring that all authors worked together on at least one study. A third author was also assigned to each study in case of disagreements that could not be resolved through consensus.

For compiling evidence, two aspects of the PMP were evaluated: 1) the quality of the PMP, and 2) the level of evidence for the PMP. The quality of the PMP relates to whether or not the findings of the studies are in agreement with the hypotheses and/or threshold cut-off values. Quality ratings for Paper III were based on a criteria list adapted from Prinsen et al.[220] and are provided in Table 3 of Paper II. Briefly, ratings were deemed sufficient, indeterminate or negative if the results were in agreement, uncertain or not in agreement, respectively. For reliability, for example, if all studies found their respective knee JPS tests to have ICC values $\geq$ 0.70, then the quality of reliability for knee JPS tests would have been rated as sufficient. Level of evidence ratings were based on the methodological quality of the included studies and are thus linked to the RoB ratings. The criteria used for Paper III were adapted from Kroman et al.[221] and are provided in Table 4 of Paper II. The possible ratings were strong, moderate, limited, conflicting or unknown. For example, if just one study for a particular PMP received an RoB rating of very good, i.e. low risk of bias, then the level of evidence was rated as strong.

Table 4. Operational definitions of the psychometric properties included in the systematic review and meta-analysis of this thesis (Paper III). Adapted from the COSMIN[222] recommendations except where indicated.

Psychometric property	Definition
Reliability	
Test-retest reliability	The degree to which errors for individuals who have not changed are the same between testing sessions over time.
Intra-session reliability	The degree to which errors for individuals who have not changed are the same between trials within the same testing session.
Measurement error	Systematic and random error of outcomes not attributed to true change.
Criterion validity	
Comparison to 'gold standard'	The degree to which the outcomes reflect those of a 'gold standard'.
Predictive validity[a]	The degree to which the outcomes at one time point predict other outcome measures at a later time point.
Concurrent validity[a]	The degree to which similar tests provide similar outcomes.
Hypothesis testing	
Convergent validity[a]	The degree to which the outcomes are similar to those of other outcome measures.
Discriminative validity[a]	The ability of the outcome measure to discriminate between the injured and non-injured side of the same individuals.
Known-groups validity[a]	The ability of the outcome measure to discriminate between groups hypothesised to differ on the outcome measure.
Responsiveness	
Criterion approach	The degree to which change in the outcomes over time reflect those of a 'gold standard'.
Between other outcome measures	The degree to which change in the outcomes over time reflect those of other outcome measures.
Between subgroups	The ability of the outcome measure to discriminate between groups thought to differ on the outcome measure over time.
To intervention	The ability of the outcome measure to detect change over time following an intervention.

[a]Adapted from other sources[223, 224] than COSMIN.

COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments.

Novel knee JPS tests

For Paper IV, a hand-held trigger used by the participants provided time points at which knee angles were extracted from kinematic data to provide the target and reproduction angles. All other events not based on the hand-held trigger for Paper IV and V were set using automated scripts based on either knee angles or knee angular velocities. For example, knee extension/flexion exceeding 1°/s from the start position set an event for the start of the movement phase. All events were checked manually by the lead researcher and either removed, added or adjusted when deemed necessary. Removal of events included instances when participants adjusted their knee position which created double start events for the same movements. Addition of events included when participants forgot to press the trigger button but kinematic data showed appropriate performance and a static position in the target or reproduction angle. Adjustment of events included when participants had pressed the trigger button prior to cessation of movement. In total, only a small percentage of events were edited.

Brain imaging

Batching, pre-processing and data analysis was performed in SPM12 (Wellcome Department of Cognitive Neurology, London, UK) run under MATLAB R 2016 b (MathWorks, Inc., Natick, MA). Visualization of statistical maps and calculation of percent of BOLD signal changes were performed using SPM12 and MarsBaR, respectively. Prior to sub-analyses, data were pre-processed using the following steps: slice timing correction, movement correction by unwarping and realigning to the first image of each volume, normalization to a sample-specific template (using DARTEL[225]) and affine alignment to Montreal Neurological Institute standard space and smoothing with an 8-mm full width at half maximum (FWHM) Gaussian kernel. The final voxel size was 2 × 2 × 2 mm. The first-order analyses included the experimental conditions as regressors of interest in the general linear model, convolved with the haemodynamic response function. Six realignment parameters (rotations and translations) were included as covariates of no interest to account for movement artefacts. Three conditions were defined for contrasts: 1) *JPS* - onset when knee angular velocity towards the reproduction angle was first > 1°/s from the start position and cessation when knee flexion was next < 1°/s, 2) *Flex* - onset when knee angular velocity during flexion to 100° was first > 1°/s from the start position and cessation when the knee angle reached 65°, and 3) *Rest* - the duration of the resting baseline condition (15 secs) in the start position with no movement. Subsequently, the following contrasts were set up for each participant: 1) [*JPS* > *Rest*] and 2) [*Flex* > *Rest*].

Statistical analyses

For Paper I, IV and V, all between-group analyses compared ACL-injured legs to the non-dominant legs of asymptomatic controls and the asymptomatic legs of the ACL groups to the dominant legs of controls. These comparisons were chosen as a more stringent analysis than if comparing the ACL-injured legs to the dominant legs of controls on the assumption that, if a difference was to exist, the dominant legs of controls would be more likely to perform favourably compared to the non-dominant legs.

Participant characteristics

For each primary research paper (I, IV and V), group means and standard deviations (SD) were calculated for age, body height, body mass, and body mass index (BMI), as well as for time since injury and reconstruction when applicable. Also, sex distribution was provided for each group. For Paper I, one-way ANOVAs with Bonferroni post-hoc tests compared between groups for age, body height, body mass and BMI. Kruskal-Wallis tests compared Tegner current activity level and Lysholm score between all groups. For Paper IV, Mann-Whitney U tests compared between groups for age, body height and body mass. A Chi-square test compared sex distribution. Also, Kruskal-Wallis tests with Dunn-Bonferroni post-hoc tests compared Tegner current activity level, IKDC and Lysholm scores. For Paper V, a one-way ANOVA compared between groups for body height and body mass, as well as for months since reconstruction between ACL groups. A Chi-square test compared sex distribution. Kruskal-Wallis tests with Dunn-Bonferroni post-hoc tests compared age, Tegner current activity level and Marx activity score between ACLR groups and CTRL. Mann-Whitney U tests compared Tegner pre-injury activity level, IKDC, Lysholm and TSK between L-ACLR and R-ACLR groups.

One-leg rise test statistics

For Paper I, performance and kinematic variables were statistically analysed using non-parametric statistics due to non-normally distributed data as assessed visually using graphs and with Shapiro-Wilk tests. Thus, for between-group comparisons, Kruskal-Wallis tests with post-hoc Dunn-Bonferroni pairwise comparisons were applied. Also, we compared cumulative percentages for total repetitions between groups using Kolmogorov-Smirnov tests to understand the distribution across groups. For within-group (between-leg) comparisons, Wilcoxon Signed Ranks tests were used and effect size estimates were provided. Within-session reliability of the knee kinematic variables was assessed for repetitions 2-11 using an Intraclass Correlation Coefficient (ICC) with a two-way mixed model using the mean of the repeated measures and absolute agreement. Classification of ICC values for interpretation of reliability was done in accordance with those suggested by Fleiss[226]: < 0.40 = poor, 0.40-0.75 = fair to good, > 0.75 = excellent. The standard error of measurement (SEM) was also provided as an estimate of the error in the units of measurement.

Meta-analyses statistics

Meta-analyses were performed when appropriate data were available from at least three studies rated as having doubtful RoB or better. Studies with an RoB rating of inadequate were therefore omitted from meta-analyses. Meta-analyses can be performed using a fixed-effects or random effects model. A fixed-effects model assumes that all differences in the observed effects are due only to sampling error.[227] A random-effects model, however, considers effect sizes to differ from study to study due to factors such as participant age. A random-effects model was used in Paper III due to, e.g. the different ages of the included ACL populations. Summary measures for meta-analyses include the standardised mean difference (SMD) and the mean difference (MD). The SMD allows for the outcome measure to be measured in different units by dividing the MD by the SD.[228] Using the MD based on the same measurement unit allows for increased interpretability of the results. We included only absolute error (AE) as an outcome variable as this was the most commonly reported and thus MD was used for all meta-analyses. Group means and SDs were entered into the RevMan software. When only medians with measures of dispersion were provided, means and SDs were calculated based on a previously reported method.[229] The I^2 index is also reported in such analyses in percent as an indication of statistical heterogeneity across studies.[228] Results of greater heterogeneity are expected to be less generalisable to similar populations. An approximate guide for the evaluation of heterogeneity based on I^2 has been provided by the Cochrane group:[230] 0-40% = might not be important; 30-60% = may represent moderate heterogeneity; 50-90% may represent substantial heterogeneity; 75-100% = considerable heterogeneity. Evaluation is however complex and a number of factors should be taken into consideration.

Knee JPS test outcome variables

Common outcome variables for knee JPS tests are constant error (CE), AE and variable error (VE). For CE, the difference between the TA and RA is calculated for each trial taking into account the direction of error, i.e. positive or negative. Due to the different direction of movement for the novel knee JPS tests of this thesis, calculations were adapted so that a positive and negative CE indicated an overshoot and an undershoot of the TA, respectively. The AE was calculated as the absolute value of the CE without considering the direction of the error. Mean CE and AE were calculated for the respective TA condition and leg. Calculation of VE was based on the mean RA using the formula:

$$\mathrm{VE} = \sqrt{[\sum (X_i - M)^2 / N]}$$

where: √ = the square root, ∑= the "sum of", X_i = score of the ith trial, M = the mean reproduction angle, N = the number of trials.[231]

For Paper IV, AE and VE were used for statistical comparisons, whereas CE was used only to provide an understanding of whether the groups tended to overshoot or undershoot the TA. This was done because CE can provide misleading information about the ability of individuals to reproduce the TA. Due to non-normal distribution, all data was log-transformed to enable parametric statistics which increases statistical power compared to performing non-parametric statistics. Test-retest reliability for both tests was statistically analysed using ICC based on a two-way mixed effects model using the means and absolute agreement according to reported guidelines.[232] Classification of ICC was in accordance with Fleiss[226] as previously described here. The SEM was calculated to provide an estimate of absolute reliability in the same value as the outcome measure by taking the square root of the mean square error term from the ANOVA. Minimum detectable change (MDC) was also calculated as an estimate of the amount of change considered relevant between testing sessions as a product of the formula

MDC = $(1.96 \times (\sqrt{2}))$ x.[233]

For between-leg analyses. i.e. between-groups and within-groups, repeated measures ANOVAs were applied for AE and VE separately. Effect sizes were also provided. For Paper V, only AE was used as the main outcome variable for the knee JPS test. Non-normal data distributions were confirmed and thus data was log-transformed. Independent samples t-tests were used to compare between groups.

Brain imaging analysis

Group analyses were based on flexible factorial models of the [*JPS* > *Rest*] and [*Flex* > *Rest*] contrasts from each participant, including participant, group (two levels, ACLR and CTRL), condition (two levels, *JPS* and *Flex*) and the interaction (group × condition) as factors. The main effect from condition ([*JPS* > *Rest*] > [*Flex* > *Rest*]) and the interaction (group × condition) was analysed (family-wise error corrected, 0.01; voxel limit 15). Any brain regions with significant activation for these analyses were further analysed by calculating the percent of BOLD change during the *JPS* condition (i.e. the original beta) in the significant region compared to the overall mean brain activity of the session. Correlations between knee JPS errors and brain response (percent of BOLD change) were assessed using Spearman's rho based on the non-normally distributed original JPS data.

Results

Background data of all participants

No groups included in between-group comparisons in any of the primary research papers of this thesis differed significantly regarding age, sex distribution or body height. The only groups to differ for body mass and BMI were those of Paper I, for which the CTRL group had lower body mass (P = 0.03) than ACLD and lower BMI than both ACLD (P < 0.01) and ACLR (P = 0.01). For Paper I, the CTRL group reported a significantly greater Tegner current activity level and Lysholm score than ACLD (P = 0.00 for both) and ACLR (P = 0.01 and P = 0.00, respectively). The ACL-injured groups did not differ significantly for these outcomes. For Paper IV, the CTRL group reported a significantly lower Tegner current activity level than ACLR and ATHL (P = 0.00 for both). The ACLR group scored significantly lower than CTRL and ATHL for both IKDC and Lysholm scores (P = 0.00 for all comparisons). No other significant differences were found for the questionnaires. For Paper V, no differences were found between the three groups for Tegner current activity level or Marx activity rating. No significant differences were either found between ACLR groups for the other questionnaires.

Knee function in the very long term after ACL injury (Paper I)

One-leg rise test results

Performance

Summary statistics for each group and leg regarding total repetitions, group percentages of those completing the maximum 50 repetitions, those who failed to complete any repetitions, and those completing less than 20 repetitions are provided in Table 5. For the injured leg, ACLD performed significantly fewer OLR repetitions than the CTRL group when they used their non-dominant leg (median difference 17, r = -0.27, P = 0.05). No other significant differences were seen between-groups or within-groups for total repetitions. Analysis of time to complete repetitions revealed no significant between-group differences, but showed that for normalised time, the CTRL group spent significantly longer to complete the *Rise* phase with their non-dominant leg compared to their dominant leg (median difference 0.62%, Z = -2.53, P = 0.01), and for absolute time the reverse was true for the *Down* phase (median difference 0.03 s, Z = 2.07, P = 0.04). No within-group differences were found for ACLR or ACLD. Figure 5 illustrates the normalised phase durations for each leg of each group for performance of the OLR test.

Table 5. Summary statistics for performance of the One-leg rise test relating to the number of repetitions achieved.

Variable	ACLR	ACLD	CTRL
		Injured/non-dominant leg	
Median (Q1, Q3)	30 (10, 49)	15 (6.5, 33.5)*	32 (12, 50)*
Max 50, %	24.2	13.5	36.4
None, %	6.1	8.1	6.1
< 20, %	33.3	59.5	36.4
		Non-injured/dominant leg	
Median (Q1, Q3)	20 (11, 49.5)	21 (3, 39.5)	37 (18, 50)
Max 50, %	24.2	21.6	48.5
None, %	6.1	13.5	0
< 20, %	48.5	45.9	27.3

*Significant difference (r = -0.27, P = 0.05).

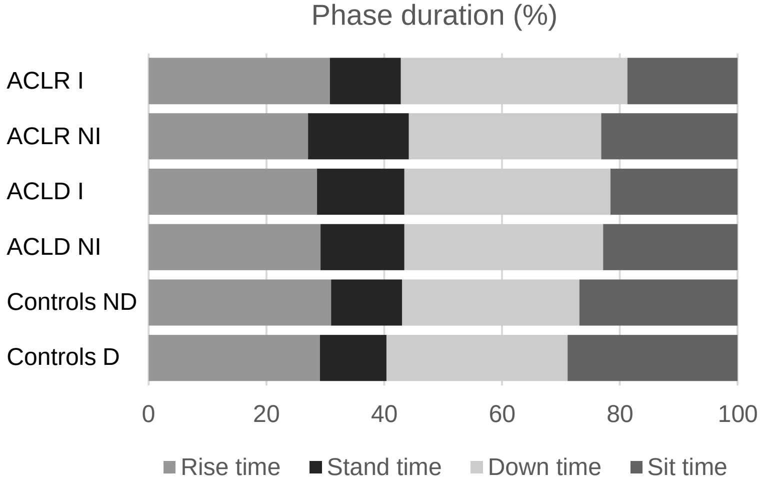


Figure 5. An illustration of the normalised phase durations for each group and leg for performance of the One-leg rise test. ACLD, anterior cruciate ligament-injured treated with physiotherapy only; ACLR, anterior cruciate ligament-reconstructed; D, dominant; I, injured; ND, non-dominant; NI, non-injured.

Knee kinematics

For between-group comparisons, ACLD showed significantly greater knee abduction maximum during the *Rise* phase compared to ACLR for both their injured leg (mean difference 2.6°, r = -0.33, P = 0.04) and their non-injured leg (mean difference 3.4°, r = -0.36, P = 0.03), as well as compared to CTRL for their non-injured leg (mean difference 3.6°, r = -0.32, P = 0.02). ACLD also performed the *Down* phase with significantly greater knee abduction maximum compared to ACLR for their injured leg (mean difference 3.7°, r = -0.32, P = 0.03) and compared to CTRL for their non-injured leg (mean difference 3.1°, r = -0.31, P = 0.04). No other between-group differences were significant. For within-group (between-leg) comparisons, ACLR performed the *Down* phase with significantly greater knee abduction maximum for their non-injured leg compared to their injured leg (mean difference 1.04°, Z = -2.11, r = -0.39, P = 0.04) and significantly greater knee adduction for their non-injured leg compared to their injured leg (mean difference 1.95°, Z = -2.04, r = -0.38, P = 0.04). No other within-group differences were significant. All knee kinematics of the OLR during the *Rise* and *Down* phases showed excellent within-session reliability for all groups and both legs (see Table 6 for ranges across groups for each phase and variable).

Table 6. Ranges of intraclass correlation coefficients (ICC) with 95% confidence intervals (CI) and standard error of measurement (SEM) across groups and legs for knee abduction and adduction maximum and range, as well as knee movement units for the *Rise* and *Down* phases of the One-leg rise test.

Phase and variable	ICC	95% CI	SEM (°)
Rise phase			
Knee abduction maximum	0.99-1.00	0.99-1.00	1.03-1.37
Knee adduction maximum	0.99-1.00	0.98-1.00	1.04-1.57
Knee abduction/adduction range	0.97-0.99	0.95-1.00	1.57-1.86
Knee movement units	0.81-0.93	0.67-0.97	0.98-1.24
Down phase			
Knee abduction maximum	0.99-1.00	0.99-1.00	0.93-1.46
Knee adduction maximum	0.99-1.00	0.98-1.00	0.99-1.60
Knee abduction/adduction range	0.98-0.99	0.97-1.00	1.52-1.95
Knee movement units	0.85-0.92	0.74-0.96	1.10-1.43

Existing knee JPS tests (Paper II and III)

The literature search detailed in Paper II yielded 2527 different studies. Following title and abstract screening, 462 full texts were screened for eligibility to the systematic review series detailed in that paper. Eighty studies were subsequently deemed eligible for inclusion in Paper III. These studies included 119 knee JPS tests, 112 ACL groups and 2475 participants. Approximately 72% of ACL groups had undergone reconstruction, 70% of participants were males and mean age was 28 years. The most common type of knee JPS test involved passive movement to the target angle with active movement to the reproduction angle (45%), followed by tests with only active movements (21%) and only passive movements (16%). The most common body position was seated (62%), followed by side lying (13%), supine (12%) and standing (7%). The most common equipment was an isokinetic dynamometer (40% of tests) and the ipsilateral leg was used to reproduce the target angle in 85% of tests. The most common starting knee angle was 90° (39%) and target angle was 30° (32%). The majority of tests involved movements of extension towards both the target angle and the reproduction angle (51%). Memorisation time of the target angle was poorly reported across studies but typically ranged from three to five seconds. Knee angular velocity was not reported for the majority of active movements, most likely because this is hard to standardise, and was very mixed among those that did report, but commonly ranged from 2°/s to 5°/s. The most commonly reported outcome variable was mean AE, with CE and VE being less common. The number of trials typically ranged from three to six. To summarise, if compiling these findings, the most common knee JPS test in the literature would seated in an isokinetic dynamometer with the tested leg at a starting angle of 90°, passive movement at an angular velocity between 2°/s and 5°/s towards a target angle of 30°, five seconds memorisation time and active movement at a self-selected angular velocity to reproduce the angle. Five trials are performed per leg with the mean AE used as the main outcome variable.

Quantitative analysis

Following assessment of RoB at the outcome level for each study and PMP, sufficient data were available from studies of doubtful, adequate or very good quality to perform meta-analyses for known-groups validity, discriminative validity and responsiveness to intervention. The results of all main analyses, sensitivity analyses for quality (only studies with an RoB rating of adequate or very good) and subgroup analyses based on test procedure are provided in Table 7. Briefly, known-groups and discriminative validity showed overall sufficient quality due to significantly greater knee JPS errors for ACL-injured knees compared to asymptomatic knees of controls and their own contralateral knees, respectively. Sensitivity analyses revealed that when including only studies of higher quality (low RoB), between-group differences tended to be either enhanced or were similar. Subgroup analyses for test procedure revealed that, in general, tests with solely passive procedures resulted in greater differences than those which included active movements. Insufficient quality was however found for responsive to intervention based on the results from six studies.

Table 7. Results of the meta-analyses regarding known-groups validity, discriminative validity and responsiveness based on absolute error.

Analysis	Studies	P value	Favours	MD (°)
		Known-groups validity		
ACL-injured vs. CTRL	18	< 0.00001	CTRL	0.70
Sensitivity analysis (quality)	4	0.0001	CTRL	2.97
Subgroup analysis (P-P)	5	< 0.00001	CTRL	1.59
Subgroup analysis (P-A)	11	NS	None	0.61
Subgroup analysis (A-A)	4	NS	None	0.26
ACLD vs. CTRL	8	0.04	CTRL	0.83
Sensitivity analysis (quality)	3	< 0.00001	CTRL	3.56
Subgroup analysis (P-A)	6	< 0.00001	CTRL	0.23
ACLR vs. CTRL	13	0.0004	CTRL	0.65
Subgroup analysis (P-P)	4	< 0.00001	CTRL	0.97
Subgroup analysis (P-A)	7	< 0.00001	CTRL	1.20
Subgroup analysis (A-A)	4	0.002	CTRL	0.26
ACLD vs. ACLR	3	< 0.0001	CTRL	0.32
Subgroup analysis (P-A)	3	0.02	CTRL	0.24
		Discriminative validity		
ACL-injured vs. ACL Contra	23	0.0003	Contra	0.67
Sensitivity analysis (quality)	6	0.002	Contra	1.55
Subgroup analysis (P-P)	6	0.003	Contra	0.78
Subgroup analysis (P-A)	14	0.003	Contra	1.01
Subgroup analysis (A-A)	8	NS	None	0.11
ACLD vs. ACLD Contra	11	0.0003	Contra	0.95
Sensitivity analysis (quality)	4	0.04	Contra	1.81
Subgroup analysis (P-P)	3	0.00001	Contra	2.25
Subgroup analysis (P-A)	8	0.01	Contra	1.06
Subgroup analysis (A-A)	4	NS	None	0.49
ACLR vs. ACLR Contra	15	NS	None	0.47
Sensitivity analysis (quality)	3	0.04	Contra	1.36
Subgroup analysis (P-P)	4	0.01	Contra	0.22
Subgroup analysis (P-A)	8	NS	None	0.95
Subgroup analysis (A-A)	4	NS	None	0.34
		Responsiveness		
Responsiveness to intervention	6	NS	None	0.67

A-A, active-active; ACLD, anterior cruciate ligament-deficient; ACLR, anterior cruciate ligament-reconstructed; Contra, contralateral; CTRL, control; MD, mean difference; NS, not significant; *P-A*, passive-active; *P-P*, passive-passive.

Qualitative analysis

The PMPs which lacked required data from three or more studies to enable meta-analyses were assessed qualitatively based on whether outcomes agreed with the hypothesis or achieved cut-off values. Results for each PMP are summarised in Table 8. Briefly, test-retest reliability and related measurement error were assessed in three studies all with an RoB rating of inadequate and thus due to an insufficient level of evidence the quality of the PMP was not estimable. Intra-session reliability and related measurement error were assessed in one study with an RoB rating of very good which found poor reliability and was subsequently rated insufficient based on a very good level of evidence. Convergent validity was assessed in 16 studies, six of which had an RoB rating of inadequate. The outcome measures of the remaining ten studies for which knee JPS tests were compared with were diverse. Correlations were not found in 90% of analyses between the outcome measures, the quality of convergent validity was deemed insufficient based on a moderate level of evidence. Responsiveness between subgroups was assessed in 10 studies, six of which had an RoB rating of inadequate. The remaining four studies did not find significant changes in knee JPS between subgroups and thus the quality of this PMP was deemed insufficient based on a moderate level of evidence. Concurrent validity and responsiveness between other outcome measures were assessed in only one study each, both with an RoB rating of inadequate and thus their quality was not estimable due to an unknown level of evidence. No studies investigated criterion validity, predictive validity or responsiveness from a criterion approach and thus their quality was also not estimable due to an unknown level of evidence.

Table 8. Overview of quality and level of evidence for the psychometric properties assessed qualitatively in the systematic review (Paper III).

Psychometric property	Studies	Quality	Level of evidence
Reliability and measurement error			
Test-retest	3	Not estimable	Inadequate
Intra-session	1	Insufficient	Very good
Criterion validity			
Comparison to 'gold standard'	0	Not estimable	Unknown
Predictive validity	0	Not estimable	Unknown
Concurrent validity	1	Not estimable	Inadequate
Convergent validity	16	Insufficient	Moderate
Responsiveness			
Criterion approach	0	Not estimable	Unknown
Between other outcome measures	1	Not estimable	Unknown
Between subgroups	10	Insufficient	Moderate

Novel knee JPS test results (Paper IV and V)

Test-retest reliability

For the NWB and WB tests of Paper IV, ICC varied depending on the test, outcome variable, leg and TA condition. However, the ICC was generally better and the SEM lower for the WB test (ICC 0.64-0.91; SEM 0.67°-1.32°) compared to the NWB test (ICC 0.47-0.78; SEM 0.97°-1.99°). Higher ICC values were generally seen when the outcome measure was AE (ICC 0.47-0.91) compared to VE (ICC 0.00-0.65) for the respective conditions. A clear trend was not seen for leg nor TA. Of all the conditions, the 65° angle condition for the WB test when using the dominant leg and AE showed the highest ICC of 0.91 (95% confidence interval [CI] 0.78-0.96) and lowest SEM of 0.67°. The MDC was generally lower for the WB compared to the NWB test when the outcome measure was AE (1.86°-3.66° vs. 2.69°-5.52°, respectively) and VE (2.33°-3.88° vs. 3.19°-4.55°, respectively). For the knee JPS test of Paper V, ICC was 0.78 (95% CI 0.34-0.93) for the dominant leg and 0.64 (95% CI 0.02-0.87) for the non-dominant leg.

ACL-injured knees compared to asymptomatic knees

For Paper IV, post-hoc pairwise comparisons revealed that, compared to ACLR, the CTRL group showed significantly greater JPS AE and VE for both the NWB and WB test for all conditions (except for 65° for the NWB test when using the non-dominant leg). No other between-group differences nor within-group (between-leg) differences were significant. For the supine knee JPS test of Paper V, although medians were greater for ACL-reconstructed knees compared to those of the CTRL group, these differences were not statistically significant.

Brain response to a knee JPS test (Paper V)

Knee JPS compared to flexion movement

Compared to the *Flex* condition, i.e. knee flexion without a JPS task, movement towards the TA during the knee JPS test resulted in significantly greater brain response in seven regions per leg, such as the precentral cortex, insula and middle frontal gyrus (see Table 9 for all significant brain regions).

ACL knees compared to asymptomatic knees

For between-group comparisons of brain response during the knee JPS test, no interactions were evident for the main analysis. However, further analyses revealed significantly greater response among R-ACLR for the precuneus (family-wise corrected, P = 0.000) as well as six other regions on the uncorrected significance level of 0.001 and voxel limit of 15, compared to CTRL and greater response was seen in the superior temporal gyrus for L-ACLR compared to CTRL.

Table 9. Brain regions with significantly greater response for: 1. *JPS* condition compared to the *Flex* condition, and 2. ACL-reconstructed (ACLR) knees compared to the corresponding leg of asymptomatic controls (CTRL).

	Voxel #	P	Z max	MNI coordinate		
				X	Y	Z
	1. *JPS* vs. *Flex*					
Right leg						
i. Precentral Cortex	459	.000	5.93	51	5	20
i. Middle Frontal Gyrus	218	.000	5.39	30	33	24
c. Anterior Cingulum*	97	.001	5.28	-9	33	21
c. Insula*	70	.002	5.09	-32	17	8
i. Insula	86	.002	5.06	36	17	8
c. Parietal Cortex	16	.005	5.03	-38	-36	36
i. Anterior Cingulum	15	.006	4.80	9	33	27
Left leg						
c. Precentral Gyrus	2488	.000	6.58	53	6	30
i. Insula	1665	.000	6.28	-32	21	3
c. Middle Frontal Gyrus	1058	.000	5.95	36	33	35
c. Medial Sup Frontal Gyrus	734	.000	5.59	12	38	38
c. Parietal Cortex	285	.000	5.35	47	-32	36
i. Middle Cingulum*	96	.001	5.03	-5	24	39
i. Inferior Parietal Lobe	40	.003	5.02	-42	-38	38
	2. ACLR vs. CTRL[a]					
Right leg						
c. Precuneus[b]	3983	.000	4.36	-6	-59	45
i. Sup Frontal Gyrus	68	.000	3.64	3	68	5
c. Anterior Cingulate Gyrus	62	.000	3.63	-3	53	14
i. Postcentral Gyrus	48	.000	3.38	32	-38	57
i. Cuneus	21	.001	3.26	11	-80	39
i. Cerebellum Crus 1	22	.001	3.24	32	-74	-29
c. Sup Parietal Gyrus	26	.001	3.20	-23	-71	45
Left leg						
i. Sup Temporal Gyrus	76	.000	3.57	-56	6	-5

[a]Significance for analysis on a peak level, not on cluster level.
[b]Region also significant on family-wise corrected (P = 0.000).
c., contralateral; *i*., ipsilateral; MNI, Montreal Neurological Institute; Sup, superior.

Correlations between JPS errors and brain response

For the left leg, greater JPS AE was significantly positively correlated with greater BOLD percent change in the ipsilateral anterior cingulum (r = 0.523, P = 0.004) and the contralateral insula (r = 0.406, P = 0.029), whereas for the right leg a similar correlation was seen for the ipsilateral middle cingulum (r = 0.364, P = 0.048), see Figure 6. No other significant correlations were found.

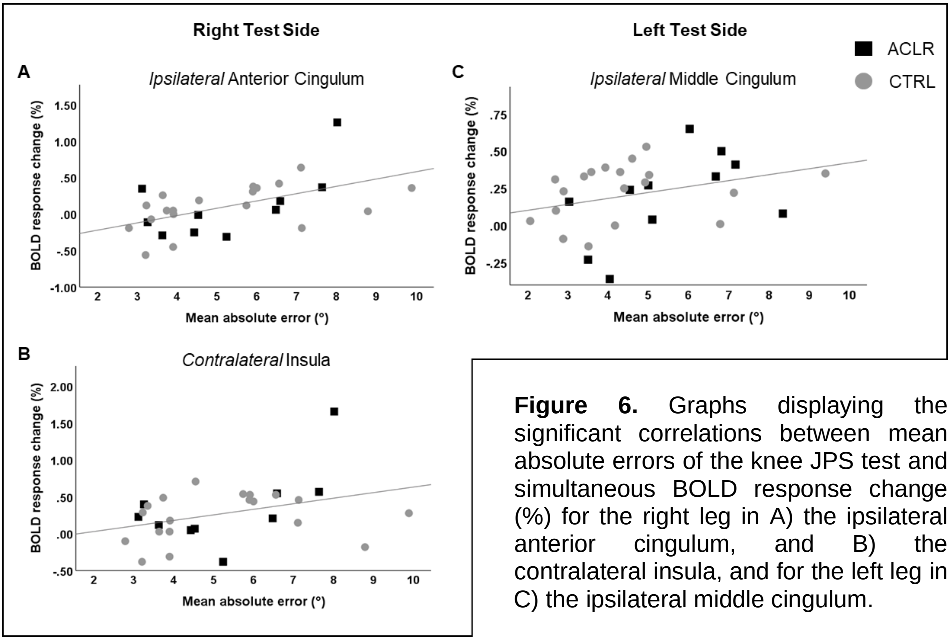


Figure 6. Graphs displaying the significant correlations between mean absolute errors of the knee JPS test and simultaneous BOLD response change (%) for the right leg in A) the ipsilateral anterior cingulum, and B) the contralateral insula, and for the left leg in C) the ipsilateral middle cingulum.

Discussion

Main findings

The main findings of this thesis indicate that ACL injury contributes to aberrant knee function two decades after injury and, according to the systematic review, also to poor knee proprioception (JPS) regardless of treatment and time since injury. Results from our novel knee JPS tests corroborate previous evidence that activity level of comparator groups is however an important factor which should be considered in analyses. Additionally, performing a knee JPS test appears to recruit brain regions that have been associated with sensorimotor processes such as stepping motions, interoception and body schema, thus indicating heightened proprioceptive demand compared to a similar movement without a knee angle matching task. Significant correlations also revealed that greater knee JPS errors seem to be associated with greater response in the cingulum and insula, suggesting an important role for these regions in such tests. Only minimal differences were seen between participants with unilateral ACL reconstruction and controls, although the most statistically significant finding was the greater response for the precuneus among ACLR.

Knee function after ACL injury - One-leg rise test

The between-group differences seen in Paper I regarding significantly fewer repetitions of the OLR achieved by the ACLD group when using the injured leg compared to CTRL indicates that the OLR test may be sensitive in elucidating functional deficiencies at the knee. The lack of within-group differences thus suggests possible cross-over effects to the contralateral leg and that using LSI would overestimate function of the injured knee, an issue which has been reported previously.[149] Thus, normative values regarding total repetitions achieved may be of value for objective assessment of OLR performance. A previous study in which individuals performed the OLR test one year after ACL reconstruction found that performing less than 22 repetitions was associated with worse self-reported quality of life two years later.[234] In contrast to our protocol, that study used a standardised seat height to ensure a knee angle of 90° when seated, thus making direct comparisons to our findings difficult. Another study among individuals with chronic knee pain found that those unable to perform 20 OLR repetitions were more likely to present with radiographic knee osteoarthritis five years later.[194] Performance of the OLR test as quantified by total repetition may thus provide a useful outcome variable to assess lower limb function and the development of cut-off values for specific populations may further enhance its usefulness. Additionally, the greater knee abduction among the ACLD further indicates the usefulness of the test as an assessment of lower limb sensorimotor control. These results are supported by previous studies showing greater knee abduction among individuals with ACL injury when performing similar movements such as one-leg half squats.[214, 215] The kinematic variables also showed excellent within-session reliability, indicating that each repetition was likely a trustworthy representation of the movement patterns for each individual. However, the lack of differences seen for knee movement units was in contrast to previous studies which found worse mediolateral knee control among individuals with ACL injury.[216, 217] Our variable did however differ compared to those utilised in the other studies and thus may require development to enhance its sensitivity. The other studies also observed such differences during hop tests and thus it is possible that these challenged knee joint stability more than the OLR. One further reason for the different results could of course be that the groups included in Paper I simply did not differ with regard to knee joint function. The ACL-injured participants of the other studies were tested within the first couple of years after injury as opposed to our long-term follow-up. It is therefore possible that this extra time facilitated improvement of joint stability to more closely match that of controls.

Given the findings of group differences, the OLR test may offer a clinician-friendly assessment of knee function that is relevant during rehabilitation from ACL injury before hop tests are feasible and perhaps among individuals who do not seek RTS. Indeed, not all individuals with ACL injury have sporting backgrounds and even those who do may not necessarily aim for RTS.[111] Nevertheless, assessments of knee function beyond the early stages of ACL rehabilitation often include one-leg hop tests designed to reflect instances in sports which potentially expose the knee to increased risks for ACL injury. Thus, current assessments of knee function may be less relevant for someone who is not planning to be involved in competitive sports. The advantage of one-leg tests, however, is that they help to isolate the functional performance of each leg separately and thus avoid the issue of reducing load on the injured leg during double-leg tests, as seen previously.[235] The OLR test therefore also avoids this potentially confounding factor. As in Paper I of this thesis, assessment of knee function beyond 20 years post-ACL injury often pertains to individuals aged 40 to 50 years given the generally young age of primary ACL injury occurrence. Interventions thus remain relevant for such a group who are hopefully active but perhaps trying to cope with early-onset knee osteoarthritis bearing in mind the reported four times higher risk compared to non-injured knees.[131] Identification of those with poor performance and deficient sensorimotor control subsequently facilitate targeted interventions to improve quality of life. A single-leg, challenging task that shows good ecological validity by being closely related to an everyday movement is thus pertinent.

Knee JPS tests after ACL injury

Systematic review and meta-analysis

The significantly greater knee JPS errors for ACL-injured knees compared to asymptomatic knees seen in Paper III of this thesis is in line with previous meta-analyses.[165, 166] The meta-analyses in this thesis, however, included 14 more studies (18 vs. 4[165]) for known-groups validity and 13 more studies (23 vs. 10[166]) for discriminative validity than the maximum number included in the aforementioned analyses. Thus, our analyses included a greater number and variety of tests and participants. Overall, the results support the hypothesis that ACL injury causes diminished proprioceptive acuity at the knee.[36, 236, 237] However, another explanation may be that individuals with poor proprioceptive acuity at the knee are more likely to injure their ACL. If so, groups of ACL-injured individuals may be overly represented by those with existing proprioceptive deficits. This is an important consideration and longitudinal studies are thus warranted to establish if this is the case.

The quality of the remaining PMPs investigated in our systematic review was less clear mainly due to a lack of high quality (low RoB) studies showing consistent results. Such analyses are, however, complex due to the many factors that can influence the results. For responsiveness to intervention, for example, the interventions implemented were very diverse both with regard to their type and duration. For example, one study assessed the effect on knee JPS of a 36-minute exercise protocol whereas several others compared before and after specially-designed rehabilitation programmes lasting several weeks. It can be questioned as to whether all interventions would be expected to induce changes to knee JPS. An explanation for the lack of change may thus have been that the interventions themselves were not adequate in inducing changes in knee JPS rather than the tests themselves not being sensitive enough to detect changes. Also, the ACL groups varied greatly across the included studies with regard to factors such as age, sex distribution, time since injury/surgery, type of surgery, and activity level. Thus, although including such a range of characteristics in the same analysis can aid in generalising the results, it becomes harder to draw conclusions about the effects of these different factors. Thus, matching of the comparator groups in each study is an important factor. Older age, for example, is believed to have a negative effect on prioprioception.[238-240] A greater activity level has conversely been associated with better proprioceptive acuity at the knee.[239, 241-246] Even sex differences have been indicated, with females showing poorer knee proprioception compared to males.[245, 247, 248] The methodologies of the knee JPS tests also varied greatly, not least with regard to the direction of movement, body position, starting and target angles, and the test procedure. As stated previously, these individual components appear to influence the outcomes of knee JPS tests and should be compared in future studies. The reporting of outcome measures was also not standardised across studies.

Overall, the participant characteristics, test procedures and outcome measures identified in the systematic review of this thesis were diverse and in many cases were not reported sufficiently in order to replicate the study. Careful matching of characteristics between comparator groups, standardisation and full reporting of testing procedures, as well as statistics based on a range of outcome measures are encouraged in future studies. This will increase the level of evidence for the quality of the PMPs of knee JPS tests and will represent a move towards a 'gold standard' test.

Novel knee JPS tests of this thesis

The novel knee JPS tests included in Paper IV and V of this thesis did not find significantly greater errors for ACL-reconstructed compared to asymptomatic knees. Each of our tests consisted of active movements which were found in our systematic review to produce generally lesser differences between legs compared to passive tests. Our subgroup meta-analysis did nonetheless find significantly greater AE for ACLR knees compared to controls based on four studies and thus the results from our tests are in disagreement with these findings. Two possible explanations for this are either that our ACL participants did not have JPS deficits at the knee or that our tests were not capable of discriminating such deficits. The significantly greater knee JPS errors for the less-active controls compared to the ACLR group of Paper IV indicates that the tests were in fact sensitive enough to elucidate differences between groups and that our ACLR group therefore did not have deficient knee JPS. Thus, the main findings of Paper IV were to corroborate evidence that activity level is an important factor regarding knee JPS and that this should be considered and accounted for when comparing between groups.

Reliability of the novel knee JPS tests was assessed for AE and VE with respect to each angle condition and leg for the WB and NWB tests of Paper IV and for AE with respect to each leg for the test in Paper V. Results from Paper IV showed better reliability for AE compared to VE and for the WB compared to the NWB test. A preference was not clear regarding leg or angle. Classifying reliability according to ICC is commonly performed according to Fleiss[226] as previously described in this thesis. Many studies base their classification on the ICC value without considering the 95% confidence interval, which has been elsewhere suggested as a more appropriate basis for classification.[232] Thus, if following this recommendation, the supine tests of Paper IV and V would be classified as poor. The WB test of Paper IV, on the other hand, would cover all three classifications (poor, fair-to-good, excellent) depending on leg and angle. The better reliability for the WB test is in line with previous results among asymptomatic individuals compared to a prone knee JPS test, although confidence intervals weren't provided in that study.[249] Given the insufficient level of evidence found in our systematic review for reliability of knee JPS test among individuals with ACL injury, this remain an area of great importance should these tests continue to be applied.

Modifiable components of knee JPS tests

Considering mixed levels of evidence and quality for the PMPs of both existing knee JPS tests and the novel tests presented in this thesis, a discussion of the difficulties in designing knee JPS tests is warranted. Relph and Herrington[239] identified 12 modifiable components of knee JPS tests that should be considered: warm-up, measurement equipment, leg, body position, test procedure, starting angle, target angle, movement direction, angular velocity, memorisation time, number of trials, and outcome measure. These components are discussed below and in relation to the findings of this thesis.

Warm-up

A warm-up is a bout of preparatory exercise which is designed to enhance subsequent physical performance.[250] It has been hypothesised that a warm-up may improve proprioception at both the peripheral and central level due to, for example, increases in nerve conduction rate and fusimotor commands, respectively.[251, 252] We found that a warm-up of any kind was rarely reported in the literature prior to knee JPS tests among individuals with ACL injury. In some studies, participants were given the opportunity to perform a practice trial for familiarisation purposes. For Paper IV of this thesis, participants practiced the requested knee angular velocity of 10°/s three times on each leg just prior to performance. Such slow movements and the few minutes of rest until beginning the test are however unlikely to have been adequate as a warm-up in this context. For Paper V, a familiarisation session was performed in the movement laboratory, but at least 30 minutes elapsed between the end of that session and the start of the fMRI protocol. Thus, the start of the fMRI protocol always began with knee flexion to 100° and an immediate return to the start position once for each leg. This may also not have been sufficient to induce the potential benefits of a warm-up on proprioception. That said, actual evidence for the benefits of a warm-up on knee proprioception is limited. Some studies have found improvement to knee JPS among asymptomatic individuals following warm ups consisting of mainly aerobic exercise such as cycling and jogging, but also stretching of the lower limbs.[252-255] However, improvements were not seen for all tests of each study and factors such as a lack of control group and visual estimation of the knee angle on an external device may have confounded results. Further research is required to establish the potential effects of different types of warm-ups on knee JPS.

Measurement equipment

Our systematic review found that 80% of all knee JPS tests used an isokinetic dynamometer to measure knee angles among individuals with ACL injury. As previously mentioned, these are convenient tools which facilitate not only the recording of knee angles but also a constant knee angular velocity. However, cutaneous feedback due to the seat and straps which are usually used to maintain body position are likely to contribute to smaller JPS errors and are often not accounted for. The ecological validity of these often seated and open kinetic chain movements can also be questioned. Other methods to record angles include goniometers and motion capture. Goniometers are available in both digital and manual forms and with arms of different lengths. One study found insufficient reliability for hand-held manual goniometry used to measure knee angles during a JPS test.[256] Another study found that even when used by trained individuals for measuring knee range of motion, goniometers of different types have poor accuracy.[257] In fact, results from that study indicate that a difference of at least 6° is required to detect a definite change in flexion or extension using goniometry. This is important for knee JPS tests where mean AE is often less than 5°. In all of our tests we used optoelectronic motion capture systems with passive markers. The main advantage of such equipment is the sub-millimeter accuracy of the measurements. However, access to such equipment is often limited to biomechanical research labs. An alternative to such expensive equipment is to use specially-designed smart-phone applications, which appear to be reliable and valid.[258, 259] This would facilitate the potential implementation of such tests in clinics. Future studies should further assess the accuracy of smart-phone applications, which is of paramount importance for the outcomes of knee JPS tests considering the small errors produced.

Leg

In Paper III, only three of 119 identified knee JPS tests involved matching of the TA with the contralateral knee. Nine tests used some form of visual estimation, e.g. indicating on a goniometer, while the remaining studies used ipsilateral reproduction. Reproducing the angle with the ipsilateral side rather than matching with the contralateral side allows for a more straightforward interpretation of the results because when using a matching task, it is unclear in which limb any potential proprioceptive deficits exist or if it is both.[207] However, one study which compared methods found contralateral matching of knee angles to be more sensitive than ipsilateral reproduction among individuals with ACLR both between legs of the same individuals and to a control group.[168] Another related consideration for any group comparison of knee JPS tests is that of leg dominance. Questionnaires have been developed to ascertain foot preference.[260, 261] However, defining leg dominance is often achieved simply by asking which foot the individual would prefer to kick a ball with, as used for Paper I, IV and V in this thesis. This can be somewhat misleading bearing in mind that individuals may change dominance depending on the task.[262] In fact, more than half of males have been shown to change their preferred leg for jumping compared to kicking a ball.[262] Thus, task-specific determination of leg dominance may be recommended in future knee JPS tests. With regard to individuals with ACL injury, there is most often a mixture of individuals who have injured their dominant side and non-dominant side. In fact, some individuals may change dominance after ACL injury. In the studies included in the systematic review of this thesis, the control leg for known-groups analysis was not consistent regarding dominance and in many cases was not even stated. Reporting of dominance for ACL groups was also very poor and is relevant for discriminative analyses. Whether dominance plays a role in knee JPS outcomes remains to be determined. Two studies have found no difference between legs for right-side or left-side dominant healthy individuals when performing similar passive knee JPS tests using a dynamometer.[263, 264] Nevertheless, future studies including between-groups analyses should be encouraged to account for potential effects of dominance and further studies investigating the effects of dominance on knee JPS are warranted.

Body position

A seated position was found to be the most common for knee JPS tests among individuals with ACL injury in our systematic review. This is likely due in part to the common use of isokinetic dynamometers, for which a seated position is most often used. Other positions included side lying, supine lying, standing, reclined and prone. For our tests, we chose a supine position to enable simultaneous MRI and a standing position to enhance ecological validity. We found mixed reliability depending on the various angles and legs, but smaller errors for the standing (WB) test compared to the supine (NWB) test for Paper IV, which corroborates previous evidence among asymptomatic persons.[249, 265-267] There is however limited evidence comparing different body positions on knee JPS test outcomes after ACL injury and studies involving asymptomatic individuals have shown conflicting results as to whether a prone compared to a seated test is more reliable.[207, 268, 269] Further research is thus needed to establish the reliability and validity of different body positions on knee JPS test outcomes among individuals with ACL injury.

Test procedure

Subgroup meta-analyses in Paper III revealed that greater differences were generally seen for tests that included passive movements rather than those with only active movements. However, specific statistical comparisons were not performed between test procedures and factors such as differences between the other components of the tests may have contributed to these results. Previous reports indicate that JPS is more accurate when using active compared to passive movements for the upper extremities[270, 271] and knee joint,[207] thus reducing absolute differences. However, the phenomenon of muscle thixotropy in assessments of position sense is often not considered.[29] Thixotropy describes the state of the muscle with regard to prior contraction and changes in length, thus relating to warm-ups.[29, 272] Briefly, in the sarcomeres of resting muscle, cross-bridges between actin and myosin form and become more stable over time. The muscle subsequently increases in stiffness and tension.[273] If the muscle is stretched, these cross-bridges detach but form again once the muscle is in a resting state at its new length. Upon subsequent shortening of the muscle, the cross-bridges prevent shortening of the muscle fibres and they become slack. These mechanisms thus result in two opposing resting states of muscle fibres: 1) stiffness in response to stretch, or 2) compliance due to slack.[274] The consequences for JPS are such that if muscles are in a state of stiffness they will be more sensitive to stretch than when slack.[274] The outcomes of passive JPS tests are thus likely to be affected by the thixotropic properties of the muscles associated with the joint.[29] Movements of active force generation are however not likely to be influenced by the effects of thixotropy.[274] Subsequently, experiments have indicated that if the muscle is conditioned systematically prior to testing, differences between passive and active JPS tests are no longer seen.[275, 276] Future studies should thus account for the potential effects of thixotropy on JPS outcome measures when designing experiments. The active procedures used in Paper IV and V should thus not have been effected by thixotropy, but may help explain the lack of differences seen for the ACL groups compared to the control groups.

Knee angles

Our systematic review found 90° and 30° to be the most common starting and target angles in the literature, respectively. For Paper IV and V, the target angles of 40° and 65° were used because the range from 40° to 80° has been recommended previously to be more reliable than more extreme ranges in sitting and prone knee JPS tests.[207] However, due to participant reaction time and delay in the software, actual target angles differed by approximately 5°. For the test in Paper V, we adjusted the angles at which stop cues were activated to 35° and 60° in an attempt to closer achieve the desired angles. However, there is a general lack of evidence to recommend the most reliable and valid starting and target angles among individuals with ACL injury or indeed for knee JPS tests in general. Some studies have instead based their selection of angles on more functional considerations. For example, Barrack and colleagues[97] chose a starting positon of 40° for a movement detection test as they hypothesised that the absence of afferent input from the ACL would have been most likely to be detected between the range of 30° to 40° knee flexion, although did not clarify further. Co et al.[277] also chose a starting angle of 40° for tests of both JPS and motion as they believed the range from 40° to full extension to be the most relevant in relation to the stance phase of gait. Suarez and colleagues[278] selected a 40° target angle because it is the position at which the hamstring muscles have the highest moment arm.

Alternatively, Hoshiba and colleagues[168] chose a 60° target angle because this is the angle of maximum isometric contraction of the knee extensor muscles and was hypothesised to be most affected among ACL-reconstructed individuals. It has however been suggested that the knee flexion range of 40°-60° is where muscle receptors predominate as the main source of feedback regarding knee JPS.[207] Thus, if the focus is on the effect of ACL injury on knee JPS, then it may be recommended to avoid this range. Subsequently, Relph and Herrington[279] stated that because both ACL bundles are taut between 10°-30° knee flexion, knee JPS target angles should be within this range for maximum performance. There is clearly no consensus regarding the optimal angles for knee JPS tests among individuals with ACL injury and the movement direction may also influence such decisions given the opposing muscular contractions.

Movement direction

Extension movement towards both the target angle and reproduction angle was found to be the most common method in our systematic review. The NWB and WB tests of Paper IV in this thesis had opposing movements of direction. The NWB test was towards extension, whereas the WB test was towards flexion. The WB test resulted in smaller AE across conditions. However, direct comparisons between these two tests considering only movement direction are not appropriate, in part due to the extra resistance of the WB test. Indeed, WB and NWB tests have previously been shown to not have good agreement and thus measure JPS differently.[169, 266, 280] Studies examining the effects of movement direction on knee JPS outcomes are scarce. However, one study among asymptomatic individuals across a wide range of ages found poorer knee JPS when the movement was towards flexion rather than extension.[239] Among individuals with ACL injury, less sensitivity to movement detection was also found for flexion movements.[281] One other study compared seated and prone knee JPS tests performed into flexion and extension.[282] For the prone test, good and moderate reliability was found into extension and flexion, respectively. Reliability was however poor for both directions of the seated test. The prone test also showed greater AE than the seated test, with the seated extension test producing smaller AE. Further studies are required to understand the effects of movement direction on knee JPS outcomes among different ACL-injured populations.

Angular velocity

For passive tests which use devices such as isokinetic dynamometers, it is possible to control a constant angular velocity. This is desirable regarding reproducibility, but is far more difficult to achieve during active tests. Our systematic review found that knee angular velocities for passive tests tended to range from 2°/s to 5°/s, but rationale for these choices was lacking. All of the novel tests in this thesis involved only active movements. Participants were allowed three practice attempts at maintaining a knee angular velocity of 10°/s with real-time visual feedback prior to each test. It is however unrealistic to expect individuals to maintain an exact knee angular velocity throughout 100° of knee flexion movement, let alone across several trials. Thus, if it is considered important that participants maintain a constant knee angular velocity, then such active tests are not suitable. Active tests with variable knee angular velocity will, on the other hand, have better ecological validity than passive tests which use constant angular velocities. Yet even active tests tend to be performed at much slower velocities than those experienced during sporting activities or even everyday activities such as walking.

Memorisation time

Memorisation time of the target angle was generally poorly reported across the studies included in our systematic review. Of those that did report, this tended to range between three and five seconds. The novel tests of Paper IV used approximate times of two seconds. This was chosen because longer times in the WB test were found to be strenuous during pilot testing and risked inducing fatigue. When designing the NWB test, we decided to keep this component similar to more fairly compare between the two tests. The extended memorisation time of eight seconds for the fMRI protocol was deemed necessary for brain imaging analyses and allows for future comparisons to this part of the test, which we hypothesise to require proprioceptive demands. Whether or not memorisation time has any influence on JPS errors for these tests is unclear. A previous study involving asymptomatic individuals found no differences in knee JPS errors between memorisation times of 3, 6, 9 and 12 seconds.[283] However, only two trials of each time interval were performed. Further studies investigating the potential effects of this component on outcomes are thus warranted.

Number of trials

As found in our systematic review, the number of knee JPS trials was most often three to five. For our WB and NWB tests of Paper V, we decided to include five trials per angle, per leg. For the fMRI protocol, this was increased to eight repetitions per angle, per leg to improve statistical power for brain imaging analyses. Very few studies have investigated the number of trials required to achieve reliable results. However, Selfe and colleagues[284] assessed exactly this among individuals with patellofemoral pain syndrome and found that five trials were adequate for active tests, whereas six trials were required for passive tests. However, among individuals after stroke, one study indicated that even 10 trials would fail to detect 20% of individuals with deficits in knee JPS.[285] Thus, the number trials required for stable and reliable results may depend on the type of knee JPS tests and the characteristics of the study population and requires further investigation.

Outcome variable

The most common outcome variable reported in the knee JPS literature was AE. Greater reliability for AE compared to VE was found in Paper IV for all conditions across both tests. This is supported by previous studies among asymptomatic individuals for seated and prone tests,[207] as well as a standing test.[286] Reliability aside, each of these three outcome variables provide different information. Reporting CE indicates accuracy and systematic error regarding whether or not participants consistently undershoot or overshoot the target angle.[287-289] It can however provide misleading information regarding errors when using the mean from multiple repetitions.[207] For example, if a participant was to undershoot a target angle by 10° for two trials and overshoot by the same amount for two further trials then the mean CE would indicate excellent JPS when in fact the individual was a long way from the target angle each time. This issue is resolved by AE because the direction of error is not considered. In the previous example the individual would thus achieve a poor mean AE of 10° rather than a perfect 0° as for CE. Although AE may in such circumstances provide a truer estimation of accuracy, neither CE nor AE account for the variance in the error scores. Providing VE accounts for this by providing an indication of the consistency of performance.[287, 288] The advantage of VE is best considered from a practical perspective. If an individual with knee pain who attends a physiotherapy clinic shows undesirable and highly variable knee movement patterns, for example, it may be a challenge to understand the specific underlying issue and design an intervention. If the undesirable movement pattern is in contrast very consistent (small VE), it may be easier to identify potential areas of weakness and design a more targeted intervention. An illustration of how different outcomes can influence each of these outcome measures is provided in Figure 7. Considering the different but useful information gained from each, it seems prudent to report CE, AE and VE in future studies investigating JPS.

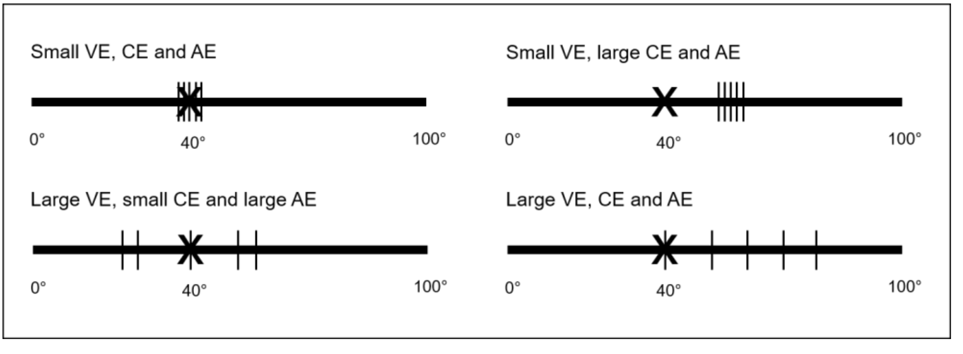


Figure 7. Illustrations of how performance can affect the outcome variables of variable error (VE), constant error (CE) and absolute error (AE) in relation to the knee JPS tests of this thesis. Knee target angle is denoted by a cross at 40° and five reproduction angles are denoted by vertical lines. This figure has been modified from Röijezon and colleagues.[287]

Brain activity related to knee proprioception

Brain response during a knee JPS test

Greater brain response was found for a number of brain regions when performing knee flexion towards the reproduction angle compared to knee flexion without a knee angle reproduction task. This was assessed depending on leg side to account for potential differences due to leg preference. Thus, the brain response of two groups of combined ACLR and CTRL participants were analysed separately. The area with the most activated voxels, which was found for the left-side, was the contralateral precentral gyrus. This area was also found to be recruited bilaterally during a single-joint knee JPS task among asymptomatic individuals by Callaghan and colleagues.[290] It forms part of the cerebral cortex and contains the primary motor cortex as well as the supplementary motor cortex, which are involved with the control[291] and planning[292] of voluntary movements, respectively. A meta-analysis also found evidence for bilateral activation related to body representations and body schema.[293] Body schema was first introduced by Head and Holmes[294] as one of two different types of body representation. Contrary to body image, which they suggest as being created using primarily visual exteroception, body schema states that alterations in body position build a postural model based on afferent and efferent information that is constantly updated on the ‘plastic schema’. They further implicate the cortex as an area where the new sensations are processed in relation to the existing model. In support of this, a study including a foot position matching task among asymptomatic individuals found recruitment of the right parietal and frontal cortex.[295] Our study adds further evidence to this due to the activation of the contralateral parietal cortex for both test sides during our knee JPS test. Another relevant role for which the parietal cortex has been associated is that of switching from one task to another.[296-300] For our *JPS* condition, we analysed brain response from when participants received instructions to move towards the reproduction angle until they ceased movement. This movement occurred just two seconds after returning to the start position from the target angle. Considering the BOLD response can take at least ten seconds to return to baseline,[296] it is possible that the observed greater response for the parietal cortex may indicate a switch to a more demanding proprioceptive task. Other regions that have also been found to be recruited when switching task and which were found to show greater response in our study include the insula[299] and right middle frontal gyrus.[296, 299]

The ipsilateral insula was recruited for both test sides and the contralateral insula for the right test side. In addition to task switching, the insula has been associated with functions relevant to our paradigm such as e.g. stepping motions[301] and interoception.[302] Interoception was originally a term used more specifically to indicate visceral sensations,[303] but has since become more widely used to encompass multimodal integration of sensations[304] and even proprioception.[305] Barret and Simmons[306] introduced the Embodied Predictive Interoception Coding (EPIC) model, which describes active inference of interoception related to predictive signalling (top-down processes) and prediction-error signalling (bottom-up processes). Their model suggests that the anterior insula and cingulate cortices contribute to the creation of a representation of the body based on multisensory interoceptive predictions. The significant correlations found in our study between knee JPS AE and the ipsilateral anterior cingulum and contralateral insula, as well as the ipsilateral middle cingulum for the right and left test sides respectively, are therefore particularly relevant to the EPIC model.

The right middle frontal gyrus was found to be recruited during our knee JPS test for both test sides. In addition to task preparation,[307] this brain region has been associated with the reorientation of exogenous to endogenous attentional control.[308] This may be relevant for our study when attention prior to the start of the movement will be on the external test instructions displayed on the screen but then reoriented during the movement towards the reproduction angle to more internal sensations. This reorientation is likely to be less relevant during the comparator task in this analysis, where participants are merely required to flex their leg to a fixed stop.

Effect of ACL injury on brain activity during a knee JPS test

Our main analysis did not find any significant differences in brain response between ACLR and CTRL. This analysis involved contrasting the *JPS* condition against the *Flex* condition within each group and comparing these differences in response between groups. The contrast between conditions was thus tight, with only the proprioceptive aspect of trying to reproduce the knee angle differing. Additionally, ACL participants had been divided into two groups, thus reducing statistical power. Considering these factors, we decided to further explore potential group differences by contrasting the *JPS* condition to the *Rest* condition instead. This analysis revealed significantly greater response for the precuneus at the corrected level for R-ACLR compared to CTRL. The precuneus has previously been shown to be recruited for a reaching task of the upper limb among asymptomatic individuals.[309] At the uncorrected level, six other regions for R-ACLR (*ipsilateral*: superior frontal gyrus, postcentral gyrus, cuneus, cerebellum crus 1; *contralateral*: anterior cingulate gyrus, superior parietal gyrus) and the ipsilateral superior temporal gyrus for L-ACLR showed significantly greater response compared to CTRL. These results should of course be taken with caution considering the analysis.

Comparing our results to other studies is difficult because, as far as we are aware, only Baumeister and colleagues[171] have investigated brain response during a knee JPS test after ACL injury. Even comparing to their study is not straightforward as they used electroencephalography rather than fRMI to analyse brain response. Nevertheless, their findings of significantly different brain response between ACL-reconstructed individuals and controls were only partially corroborated by the results in this thesis. In the study by Baumeister and colleagues, the ACL group showed significantly poorer knee JPS than the control group, whereas we did not find any significant difference between our groups for knee JPS errors. The ACL participants of their study had received reconstructive surgery on average 12 months previously, as opposed to 23 months for the ACL group of Paper V. Thus, given evidence of improvements in knee proprioception up to two years post-ACL injury,[310] it is possible that this extra time was beneficial in restoring knee proprioception and potential neuroplastic adaptations. However, it has been hypothesised that such changes are permanent[183] and other factors such as the JPS test or analysis methods may have also accounted for the differences in results.

One important question, should the increasing evidence of differing brain response between individuals with ACL injury and asymptomatic individuals be confirmed, is whether such differences are present before the injury or whether they occur as a result of the injury. One prospective study of male football players found less functional brain connectivity during resting state MRI among individuals who later injured their ACL compared to individuals matched for age, body height, body mass and school year who did not go on to suffer an ACL injury.[311] A similar study of female participants also found decreased connectivity in those who later went on to suffer an ACL injury.[312] Another study found significantly worse performance with regard to reaction time, processing speed, as well as visual and verbal memory among intercollegiate athletes who later went on to suffer non-contact ACL injuries compared to athletes matched for body height, body mass, age, sex, sport, position and years of experience at the collegiate level who did not later suffer an ACL injury, suggesting neurocognitive differences between these groups.[313] A recent study found more resting-state electrocortical activity for athletes considered to be of high risk for ACL injury based on performance of a drop vertical jump task compared to those considered to be at low risk.[314] Screening athletes for such factors may be considered time-consuming and expensive or perhaps not even currently accessible for many individuals. However, should the level of evidence become strong enough to be more certain of such disparities and interventions be developed to address them, then injury risk could be reduced among those most likely to have otherwise been injured. Considering the costs and time involved in post-ACL injury treatment, not to mention the increased risks for secondary injuries and early-onset knee osteoarthritis, the long-term benefits could potentially justify such measures.

Methodological considerations

Participants

Participants included in Paper I had suffered their ACL injury on average 23 years prior to testing. At such a long-term follow-up, it is impossible to obtain precise information relating to all the factors that could influence study outcomes. Thus, although all three groups were matched regarding age and sex, factors such as activity level over the life span are harder to account for but should be considered when interpreting results. Also, for each primary research paper in this thesis (I, IV and V), individuals who had undergone ACL reconstruction were included. For such individuals, reconstruction includes three main factors that should be considered when comparing to otherwise matched groups of asymptomatic individuals: 1) the injury, 2) the reconstruction, and 3) the rehabilitation.[171] Differences in each of these factors can have meaningful effects on study outcomes. It should thus be noted that the results pertaining to the original papers of this thesis may not be generalisable to other groups of individuals with ACL injury.

Concomitant injury to the meniscus has been found in up to 85% of individuals at primary ACL reconstruction.[315] Individuals with degenerative meniscal tears show impaired quadriceps strength and performance of functional tests such as hops and knee bends, as well as self-reported issues including knee pain.[316] Menisci also contain mechanoreceptors such as Ruffini endings and Pacinian corpuscles, suggesting a proprioceptive function.[317] In fact, knee JPS has been shown to improve following meniscal allograft transplantation.[318] Stimulation of the posterior horn of the meniscus even produces cortical somatosensory evoked potentials, thus showing that afferent signals are conveyed to the CNS.[319] It is thus evident that injury to the meniscus can influence outcomes regarding knee function, knee proprioception and related brain activity. The participants of this thesis were included regardless of concomitant meniscal injury and were not screened to ascertain the extent of potential trauma. The findings should therefore be interpreted with an understanding that meniscal injuries may have contributed to study outcomes.

Data acquisition

A whole-body marker set was used for the OLR test in Paper I. Kinematic analyses were however limited to only the knees partly because motion capture camera placement was not optimised for the OLR test specifically, but instead to the large test battery performed. Owing to the task itself and the stool blocking the field of vision, a number of markers were thus regularly occluded from sight. For example, the anterior superior iliac spine markers were occluded during the *Rise* and *Down* phases as participants flexed at the hips. A whole-body kinematic analysis would have allowed for analyses of further kinematic variables such as trunk lean, which has been shown to differ among individuals with knee osteoarthritis compared to asymptomatic persons during a sit-to-stand test, possibly as a strategy to unload the affected side.[320]

For Paper III, data acquisition was performed electronically by searching databases for relevant studies. The search was systematic and broad in accordance with the protocol set out in Paper II to include all articles investigating any PMP of any test of knee proprioception among either asymptomatic individuals or those with ACL injury. This was done to be able to perform several systematic reviews which are currently ongoing. It was also thought that including broad search terms would increase the likelihood of identifying studies of relevance for each individual systematic review, such as for Paper III. Yet despite such a broad search in many large and relevant databases, we identified a number of additional studies manually by searching reference lists and Google Scholar. Of course this could be considered part of our search strategy and even expected, but we had hoped to identify all relevant studies via our main databases. It serves however as a reminder that some relevant studies may not have been identified by our search methods despite our efforts.

For Paper IV, a hand-held trigger was used in order for participants to confirm the target angle and also when they had reached the reproduction angle. This was not always performed correctly, particularly for the first repetition, despite standardised instructions and the opportunity to ask questions prior to starting the test. It may thus be recommended in future protocols to include a full practice trial prior to commencing the test. In cases when trigger events were missing, knee angles were extracted based on kinematic data only when it was considered appropriate. This required curve profiles showing a clear cessation of movement at an angle deemed reasonable. Participants were also often asked during or after the test if any of the trials had been wrong and this was noted by the lead researcher. Only a small percentage of data points were subsequently missing from the final analyses.

For Paper V, we used wand markers for the greater trochanters and lateral malleoli so that the middle of our three cameras could capture the movements of all markers. It is possible that the wand markers resulted in erroneous kinematic data due to movement artefacts. The use of wand markers has however been shown to accurately replace surface markers for the anterior superior iliac spine during gait analysis.[321] To verify our own data, we assessed the position of the marker of the foot plate in relation to the knee angles and found excellent correlations. We also visually assessed knee angle curves and no anomalies were identified. Although we therefore do not have reason to believe that our kinematic data was effected by the use of wand markers, the use of at least four cameras in similar setups would facilitate the use of solely skin markers and is recommended to reduce potential movement artefacts.

An inherent issue in analysing BOLD response to a task is the approximate two-second delay in response which continues to evolve beyond ten seconds.[322] Traditionally, a block design has therefore been commonly used in such studies. Paradigms typically involve alternating between two conditions, each of which require maintenance of cognitive engagement but to contrasting stimuli.[323] Event-related designs have also been developed and allow response to single events.[324] Despite the delay in BOLD response, fMRI is capable of measuring these different events even in the presence of an overlap in response.[322] Our paradigm was not typical to either such design but was instead more suited to a standard knee JPS test protocol adapted to fMRI. We chose the movement towards to the reproduction angle during which to extract brain imaging data with the hypothesis that proprioceptive demands would be heightened during this period. These movements lasted on average 5.3 to 6.3 seconds depending on the group and leg. Choosing a different timeframe would potentially have altered our results related to BOLD response. Future paradigms should therefore attempt to adapt knee proprioception tasks to further suit typical fMRI analysis designs to facilitate improved interpretation of results.

Data processing and statistical analyses

For Paper I, the maximum of 50 repetitions was achieved by 24% and 31% of all participants for the injured/non-dominant and non-injured/dominant legs, respectively. The control group accounted for 49% of those individuals. A previous study of individuals with chronic knee pain who were approximately the same age as the participants in our study, found that up to 229 OLR repetitions were achieved.[194] Thus, the statistics relating to the total number of repetitions would almost certainly have been different had the maximum repetition limit not been applied in our study. The limit was included in accordance with a previous protocol,[197] and also because during pilot testing the OLR was reported as being very strenuous and thus we wanted to avoid potential effects of fatigue impacting on other tests in the battery.

Kinematics for the OLR test were based on up to ten repetitions per leg. The first repetition was omitted because starting body position was often more upright on the stool compared to when returning from a rise. This meant that kinematic data of participants who performed fewer than 11 repetitions for a particular leg were based on fewer repetitions. Considering that our reliability analysis included only individuals who contributed with ten repetitions, the reliability of the kinematic outcome variables for those completing fewer repetitions therefore remains unknown. This is important from a clinical perspective because it is more likely that those with difficulties during such tasks will present at the clinic. Further studies are thus required to evaluate the reliability of kinematic outcome variables of the OLR test among individuals who fail to achieve more than ten repetitions.

For each meta-analysis we also performed a sensitivity analysis when possible to account for the methodological quality (RoB) of the studies. When including only studies with adequate or very good ratings, i.e. low RoB, the MD increased for each comparison. Thus, although results from the main analyses indicated differences of < 1° in accordance with previous meta-analyses, sensitivity analyses for quality found greater differences of 2.97° for known-groups validity and 1.55° for discriminative validity. It should be noted, however, that these sensitivity analyses for quality included only five and six studies for known-groups and discriminative validity analyses, respectively. Thus, further studies with a low RoB are warranted to provide further evidence of high quality. Also for Paper III, RoB was assessed using the latest COSMIN guidelines. A number of different tools with contrasting methodologies are available for such assessment and thus this may contribute to lack of agreement between studies. The previous aforementioned meta-analyses of Relph and Herrington[165] and Kim et al.[166] used either a tool developed by the authors themselves or the Newcastle-Ottawa Scale, respectively. Relph and Herrington used a three-point grading scale for quality assessment of poor, moderate and good compared to our four-point scale for RoB (a reflection of methodological quality) of inadequate, doubtful, adequate and very good. The four common studies assessed for known-groups validity all received ratings of moderate and doubtful, respectively, and were thus rated similarly. Kim et al. used the Newcastle-Ottawa scale for quality assessment, which includes eight questions with a maximum score of nine. Studies with scores higher than five were considered of high quality, but no further distinctions were made. Their meta-analysis assessed only discriminative validity, i.e. between legs of ACL-injured persons. Two of their ten included studies were not included for discriminative validity in our analysis because the original studies had in fact only assessed known-groups validity, i.e. ACL-injured knees compared to knees of other persons. Also, two other studies which were rated by Kim et al. as having high quality were rated as inadequate in our review. Thus, if criteria for study quality differ between meta-analyses, and if quality is a factor for inclusion, this may increase the likelihood of different conclusions between studies. Of course, including all studies regardless of quality is an option, but even then sensitivity analyses for quality should also be performed.

An inherent confounding factor with all such assessments of methodological quality is that the researchers themselves grade the studies. Although the quality assessment tools aim to reduce subjectivity by asking specific questions, certain disagreements are likely to exist between assessors of the same review and between those of different reviews. The procedures used in the systematic review of this thesis aimed to reduce such subjectivity. Specifically, all five authors first piloted the RoB assessment with two studies independently. Ratings were then discussed in detail at a meeting before assessment of the remaining studies commenced. Each study was assigned two authors who assessed RoB separately using the same COSMIN checklist. It was also ensured that all possible pairs of authors worked together and that any sources of uncertainty were discussed among all individuals either during meetings or e-mail. A third author was assigned to each study in case a consensus could not be reached. A consensus was however always reach between the two assigned authors, indicating a good level of agreement. Nevertheless, further standardisation of procedures for quality assessment is encouraged to limit discrepancies between studies of the same systematic review and between systematic reviews.

For the meta-analyses of Paper III, the MD rather than the SMD was used. This was done to allow for ease of interpretability of the results and because the majority of studies had used the same outcome measure, i.e. mean AE. However, several studies were omitted from the various analyses because they reported CE and/or VE only. Had SMD been applied, it would have been possible to include more studies in the analyses. Future studies should consider the advantages and disadvantages of each method. Reporting of both methods may also be feasible in certain circumstances. Funnel plots are common tools when performing meta-analyses to identify potential publication bias. Additional trim and fill analysis can correct for publication bias if deemed present.[325] However, it has been stated that this should only be performed if criteria relating to the number of included studies, statistical heterogeneity and variance ratio across studies are met.[326] These criteria were not met in any of our meta-analyses and thus funnel plots were not performed. Publication bias may thus have influenced our results.

For Paper V, we had initially hoped to recruit individuals that had injured the same side knee. This proved not to be possible due to both a limited number of people meeting eligibility criteria and the timeframe for data collection. We therefore included a mixed group of individuals with right- and left-side ACL reconstructions. Although previous evidence suggests less lateralisation for knee movements compared to the fingers,[327] we decided to split the ACL group based on injury side so as not to potentially confound our results. For our between-group comparisons this therefore resulted in less statistical power than we had planned for and may partly explain why group differences were not as significant as we had hypothesised. Future studies are encouraged to include larger groups with the same side injury when possible.

To process and analyse brain images, common methods such as realignment to the first image of each volume were applied. However, a recent article revealed that results from fMRI analyses can differ greatly between research groups due to slight diversity in workflows.[328] In fact, the article found that of 70 independent research teams, no two teams chose exactly the same workflows to test the same hypotheses. Thus, it is possible that differences between fMRI study outcomes are likely to be at least partially accounted for by the differing data analysis methods. It is therefore important that efforts are made to standardise procedures further. Nevertheless, even using standardised methods, analysing what is happening in the brain and interpreting these observations is not straightforward. Logothetis[329] provides a number of inherent issues with fMRI, such as its difficulties in differentiating between bottom-up and top-down processes, yet states that it is the best tool at our disposal to provide insights into brain function.

Clinical implications and future directions

The OLR test is easy to implement in clinics and may be an appropriate assessment of lower extremity knee function among certain populations. If performed as in Paper I, it requires little equipment and reflects a controlled low-risk exercise similar to a sit-to-stand movement performed regularly in everyday life by the majority of people. Although a motion capture system was used to assess knee kinematics of knee abduction/adduction, trained physiotherapists should be capable of observing these movement patterns in the frontal plane. Identifying individuals with aberrant movement patterns may be useful in targeting interventions given the link between biomechanical variables of the lower limbs and post-ACL injury knee osteoarthritis.[330]

As evident in Paper III, existing knee JPS tests lack strong evidence for their sufficient reliability, validity and responsiveness among individuals with ACL injury. Indeed, the active WB and NWB tests of Paper IV further demonstrate the difficulty in developing reliable and valid knee JPS tests. However, the results of the meta-analyses indicate that knee JPS tests do elucidate greater errors for ACL-injured compared to asymptomatic knees and that passive tests rather than active tests may be most sensitive. From a clinical perspective, this information is useful because identification of ACL-individuals with aberrant knee proprioception can help to target related interventions to improve outcomes. Our results thus point towards which tests to develop further. However, many factors may have contributed to these results and further developments in knee JPS testing are clearly required before clinicians can consider them trustworthy tools of assessment. Developing normative values for both OLR performance and knee JPS tests may be of benefit for future clinical assessment rather than relying on the common method of LSI.

We remain in the early stages of understanding brain response in relation to knee proprioception post-ACL injury. Specific brain regions that have been associated with related functions were however recruited during the paradigm included in this thesis. This indicates that our test placed relevant demands on the CNS as intended and is encouraging for future investigations. Whether such brain response is effected by ACL injury remains less clear but evidence indicates certain differentiations compared to asymptomatic individuals. Training interventions to address this may thus be clinically relevant and some studies have reported evidence of relevant training effects. Neuromuscular training with real-time biofeedback, for example, has been shown to cause neuroplasticity in young female athletes.[104] It may thus be reasonable to hypothesise that similar interventions among individuals with ACL injury may result in positive neuroplasticity. The incorporation of proprioception-specific exercises should be assessed in future studies to develop targeted and effective interventions to improve rehabilitation outcomes.

Conclusions

The following conclusions were derived from the original papers of this thesis:

- Poorer knee function and greater knee abduction was evident two decades after ACL injury among individuals treated with physiotherapy alone, but not those treated with additional reconstructive surgery, for performance of the OLR test compared to asymptomatic controls. (Paper I)
- The excellent within-session knee kinematics during the OLR test indicate that individuals perform with distinct and consistent movement patterns. The OLR test may thus be a reliable assessment tool of function and movement control of the knee in the long term post-ACL injury. (Paper I)
- Based on existing knee JPS tests, strong evidence indicates that ACL-injured knees produce significantly greater errors than those of asymptomatic controls (known-groups validity) and the contralateral asymptomatic knees of the same individuals (discriminative validity). Tests of passive movements elucidate greater differences than those with active movements. (Paper III)
- In contrast, the reliability, measurement error, criterion validity, convergent validity and responsiveness of knee JPS tests remain uncertain among those with ACL injury, largely due to insufficient or conflicting evidence. Future studies should investigate the effects of the different modifiable components of such tests on all PMPs among different populations, ensuring that the methods and participant characteristics are thoroughly reported. (Paper III)
- Activity level was found to be an important factor regarding knee JPS approximately two years after ACLR as demonstrated by significantly greater errors of less-active individuals for NWB and WB tests. The lack of difference in errors between ACLR and activity-matched athletes indicates restoration of knee JPS at this time point. (Paper IV)
- Our knee JPS test recruited brain regions associated with sensorimotor processes, interoception and body schema, thus indicating heightened proprioceptive demands compared to a similar movement. (Paper V)
- Significant correlations revealed associations between greater knee JPS errors and increased response in brain regions associated with interoception and predicting errors. (Paper V)
- Subtle differences in brain response were found between ACLR and controls during reproduction of knee angles. Evidence of greater response for the precuneus in particular should be further investigated in studies including a greater number of participants and refined fMRI paradigms. (Paper V)

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Appendix

Marker sets for motion capture included in this thesis are detailed below.

Table A1. Locations of the markers used for knee kinematics of the One-leg rise test for Paper I of this thesis. Additional markers affixed to participants but not used in Paper I are illustrated in Figure A1. R/L at the start of the marker name indicates right/left.

Marker name	Marker location
SACRUM	Midpoint of the right and left posterior superior iliac spine
R/L_CRISTA	Most superior and lateral point of the iliac crest
R/L_ASIS	Anterior superior iliac spine
R/L_THIGH CLUSTER	Middle of the anterior thigh
R/L_M_KNEE	Medial epicondyle of the femur
R/L_L_KNEE	Lateral epicondyle of the femur
R/L_TUB	Tuberositas tibiae
R/L_SHANK CLUSTER	Middle of the anterior shank
R/L_L_MALL	Most lateral aspect of the lateral malleolus
R/L_M_MALL	Medial malleolus

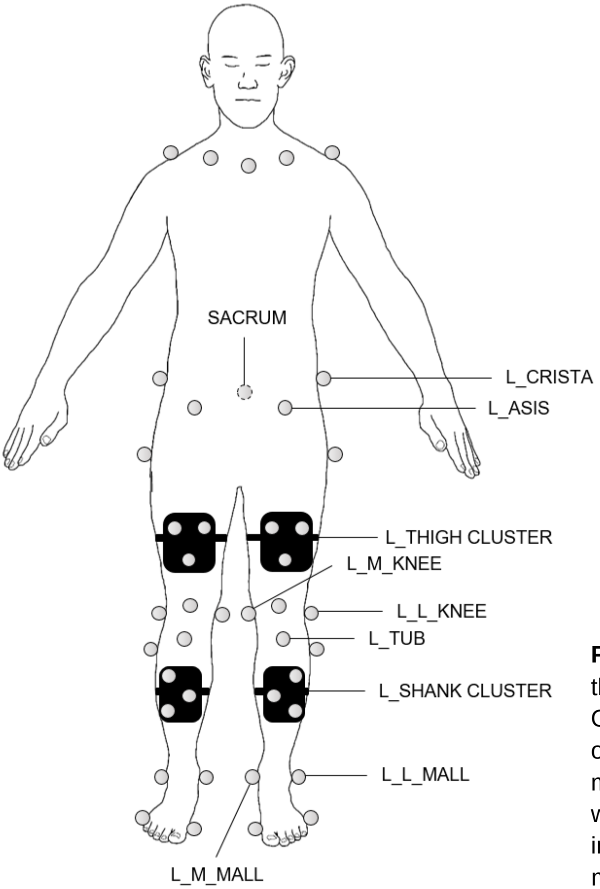

Figure A1. An illustration of the marker set used for the One-leg rise test in Paper I of this thesis. Only the markers denoted by name were used for kinematics, including the respective markers for the left side.

Table A2. Marker locations for the knee joint position sense tests of Paper IV of this thesis. R/L at the start of the marker name indicates right/left.

Marker name	Marker location
R/L_CRISTA	Most superior and lateral point of the iliac crest
R/L_ASIS	Anterior superior iliac spine
R/L_TROCH[a]	Most prominent part of the trochanter major
R/L_THIGH CLUSTER	Middle of the anterior thigh
R/L_L_KNEE[a]	Lateral epicondyle of the femur
R/L_TUB	Tuberositas tibiae
R/L_SHANK CLUSTER	Middle of the anterior shank
R/L_L_MALL[a]	Most lateral aspect of the lateral malleolus

[a]Only these markers used to provide knee angles.

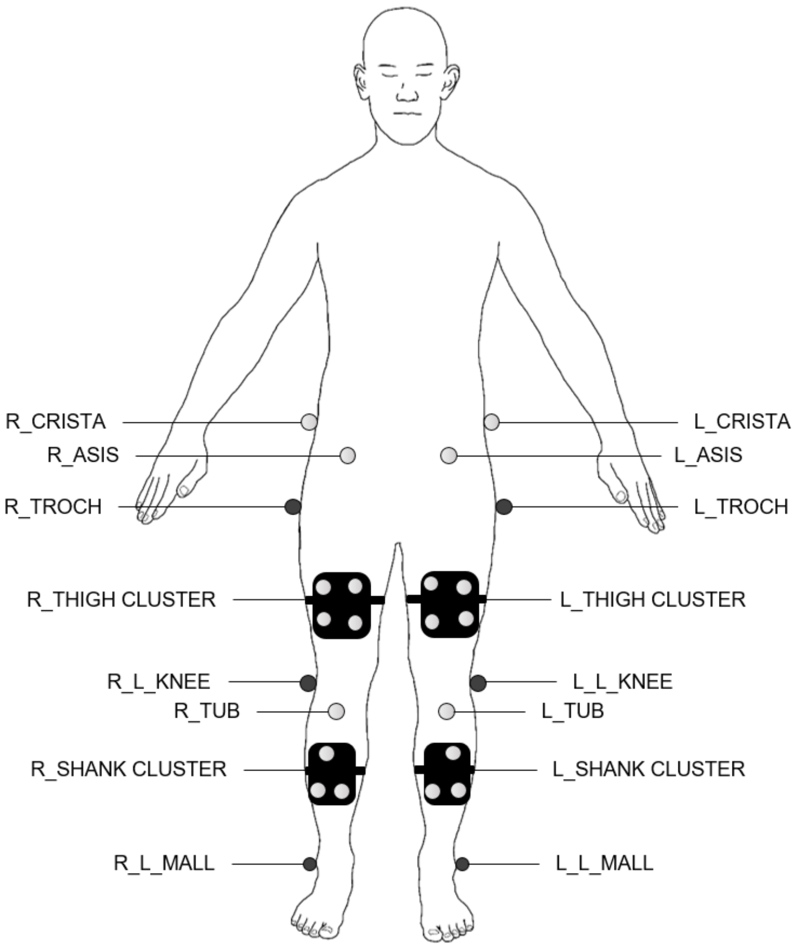

Figure A2. An illustration of the marker set used for the knee joint position sense tests of Paper IV of this thesis. Only the markers filled black were used to provide knee angles.

Table A3. Marker locations for the knee joint position sense test of Paper V of this thesis. R/L at the start of the marker name indicates right/left.

Marker name	Marker location
R/L_TROCH[ab]	Most prominent part of the trochanter major
R/L_L_KNEE[a]	Lateral epicondyle of the femur
R/L_L_MALL[ac]	Lateral foot holder in line with the lateral malleolus
L_FOOT	Proximal edge of the left sliding foot plate
R_FOOT1	Proximal medial corner of the right sliding foot plate
R_FOOT2	Proximal lateral corner of the left sliding foot plate

[a]Only these markers used to provide knee angles.
[b]Markers placed on 56 mm sticks ('wand markers')
[c]Markers placed on 46 mm sticks ('wand markers')

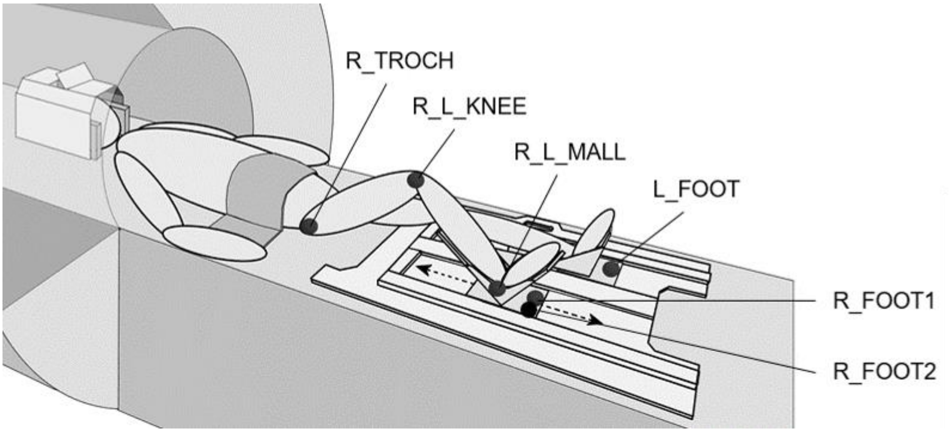

Figure A3. An illustration of the marker set used for the knee joint position sense test of Paper V of this thesis. Not seen are three markers on the left leg corresponding to those on the right leg. The R/L_TROCH and R/L_L_MALL markers were placed on sticks 56 and 46 mm in length, respectively. The R/L_L_MALL markers were affixed to the foot holders of the custom-made sliding board in line with the lateral malleolus.