# Fatigue in primary Sjögren's syndrome is associated with an objective decline in physical performance, pain and depression

R.F. Prak[1], S. Arends[2], G.M. Verstappen[2], G. van Zuiden[2], F.G.M. Kroese[2], H. Bootsma[2], I. Zijdewind[1]

[1]Department of Biomedical Sciences of Cells and Systems; [2]Department of Rheumatology and Clinical Immunology, University Medical Centre Groningen, University of Groningen, The Netherlands.

## Abstract

### Objective
Fatigue is a major complaint in primary Sjögren's syndrome (pSS). To acquire a better understanding of fatigue in pSS, we investigated objective measures of performance decline (performance fatigability). Furthermore, we evaluated the relationship of self-reported fatigue with performance fatigability and factors modulating perceptions of fatigability (perceived fatigability).

### Methods
Thirty-nine pSS patients and 27 healthy controls were included. To assess performance fatigability, force decline was measured during a sustained (124s) maximal voluntary contraction (MVC) with the index finger abductor muscle, and voluntary muscle activation was indexed using peripheral nerve stimulation. Self-reported fatigue was quantified using the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS). Pain, depression, and anxiety assessed using questionnaires and inflammatory biomarkers measured in blood were used as factors relating to perceived fatigability.

### Results
Voluntary muscle activation was reduced in pSS (p=0.030), but force decline during the sustained MVC did not differ between groups. Self-reported fatigue was significantly higher in pSS than in controls (FSS: 4.4 vs. 2.6, p<0.001). Multivariable linear regression showed that both performance fatigability (force decline) and perceived fatigability (pain and depression) were associated with the MFIS physical domain in pSS (total explained variance of 47%). Negative associations with fatigue were observed for two interferon-associated proteins: MxA and CXCL10.

### Conclusion
This study demonstrates that performance fatigability in pSS was compromised by a reduced capacity of the central nervous system to drive the muscle. Furthermore, self-reported fatigue is a multifactorial symptom associated with both performance fatigability and perceived fatigability in patients with pSS.

### Key words
Sjögren's syndrome, fatigue, muscle fatigue, central nervous system, cytokines

*Roeland F. Prak, MD*
*Suzanne Arends, PhD*
*Gwenny M. Verstappen, PharmD, PhD*
*Greetje van Zuiden, MSc*
*Frans G.M. Kroese, PhD*
*Hendrika Bootsma, MD, PhD*
*Inge Zijdewind, PhD*

*Please address correspondence to:*
*Roeland F. Prak,*
*Department of Biomedical Sciences*
*of Cells and Systems,*
*University Medical Centre Groningen,*
*Section Molecular Neurobiology, FB43,*
*Antonius Deusinglaan 1,*
*9700AD Groningen, The Netherlands.*
*E-mail: r.f.prak@umcg.nl*
*ORCID iD: 0000-0002-4729-6588*

## Introduction

Fatigue is a major complaint in autoimmune diseases including Sjögren's syndrome (1-3). Primary Sjögren's syndrome (pSS) is characterised by sicca symptoms (oral and ocular dryness) with lymphocytic infiltration of the exocrine glands. Extra-glandular involvement occurs in 40–50% of patients and may develop in almost any organ or organ system (4). Approximately 70% of patients suffer from fatigue, and for many patients this is arguably the most prominent and disabling symptom (5-8). Fatigue limits individuals in their daily activities, including work and social participation, and has a negative impact on quality of life (9-11). The importance of fatigue in pSS is demonstrated by its inclusion as one of the three domains of the EULAR Sjögren's Syndrome Patient Reported Index (ES-SPRI; 12) as well as being the primary outcome measure of a large clinical trial (13). To date, there is no effective treatment for fatigue (7, 13) and more fundamental studies are needed to identify potential targets for therapy.

Unfortunately, progress in the field of fatigue is hindered by the use of different definitions; *i.e.* fatigue as a perception or fatigue as a decline in performance. In order to facilitate studies on fatigue, Enoka and colleagues developed a conceptual framework of fatigue (3, 14, 15) (Fig. 1). In this framework, the term fatigue is reserved for the self-reported symptom which can be quantified using questionnaires and is mediated by two attributes: performance fatigability and perceived fatigability (3, 14). *Performance fatigability* is defined as an objective decline in performance measured during a prescribed task (3, 14). The concept of performance fatigability has received growing attention in clinical research (16-18). *Perceived fatigability* refers to changes in the anticipated capabilities of the performer (3, 14) and is modulated by homeostatic factors (*e.g.* pain, inflammatory cytokines) as well as psychologic state (*e.g.* depressed mood). One of the key messages of the work of Enoka *et al.* (14) is that both performance fatigability and perceived fatigability contribute to self-reported fatigue, and therefore parameters reflecting both attributes need to be measured to gain a better understanding of fatigue. In previous work on fatigue in pSS, most authors (19-21) focussed on factors related to perceived fatigability. While experimental work on performance fatigability in pSS or related systemic autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus) is lacking, changes in performance fatigability have been described in fibromyalgia (22).

Since changes in both perceived- and performance fatigability affect fatigue and are important to interpret and understand fatigue in pSS, our first aim was to objectify performance fatigability in pSS. We measured force decline during a sustained maximal voluntary contraction of a hand muscle, and electrical stimulation was applied to the innervating nerve to distinguish between performance decrements arising at the level of the central nervous system (CNS) versus the muscle and the neuromuscular junction (23). The second aim was to determine the relationship between self-reported fatigue and performance fatigability with factors modulating anticipated capabilities of the performer (*i.e.* perceived fatigability). Parameters inspired by previous research in pSS (19) and multiple sclerosis (24) were quantified as potential factors mediating perceived fatigability (pain, depressed mood, anxiety, and inflammatory biomarkers).

## Patients and methods

### Study population

This cross-sectional study included 39 patients (34 females and 5 males, aged 27-65 years) with a clinical diagnosis of pSS fulfilling the 2016 ACR-EULAR classification criteria and 27 healthy controls (22 females and 5 males, aged 27–65 years). Patients were recruited consecutively from the outpatient clinic of the University Medical Centre Groningen (UMCG) between October 2016 to March 2018. The control group was recruited from healthy volunteers who responded to local advertisements and was matched to the pSS group by age and sex. All participants had adequate hand dexterity and had no arthralgias that could limit task performance. Ex-
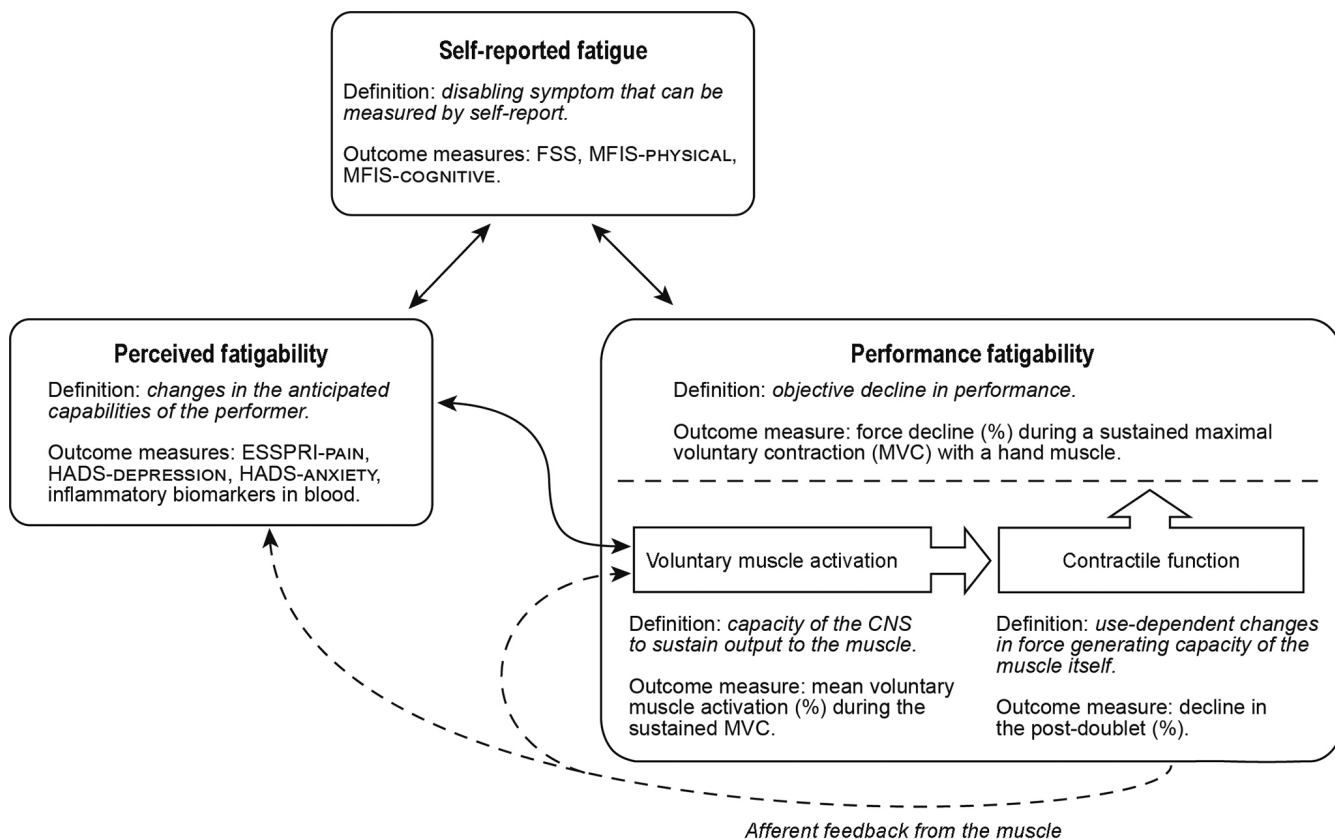
**Fig. 1.** Framework and definitions.
Conceptual framework for self-reported fatigue (adapted from Enoka *et al*. 2016). Self-reported fatigue is mediated by two attributes: perceived fatigability and performance fatigability. The two attributes may also interact as indicated by the arrows. Performance fatigability is the resultant of changes in voluntary muscle activation and use-dependent changes in contractile function of the muscle itself. The outcome measures for self-reported fatigue, perceived fatigability, and performance fatigability are shown for the present study.

clusion criteria included history of drug or alcohol abuse, psychiatric disorder, neurologic disorder, and other disorders related to fatigue. Further exclusion criteria included use of medication influencing immune function including corticosteroids, conventional disease-modifying antirheumatic drugs including hydroxychloroquine (DMARDs; <1 month prior to inclusion), or biological DMARDs (<6 months prior to inclusion). Use of analgesic medication was allowed, with exception of opioids. Experiments were designed in accordance with the declaration of Helsinki (25) and experimental procedures were approved by the medical ethical board of the UMCG. Written informed consent was obtained from all participants prior to the experiment.

*Performance fatigability*
Our first aim was to asses performance fatigability in pSS; adopting the same experimental setup and procedures

previously utilised by our lab in other clinical populations (26, 27). Participants were seated behind a desk with their elbows flexed at approximately 90 degrees and forearms resting on a raised platform. Isometric index finger abduction force was recorded from both hands using custom-made force transducers (28); Fig. 2C). Surface electromyographic (EMG) recordings were obtained from the first dorsal interosseous muscles (FDI; index finger abductor) using sintered Ag/AgCl electrodes (In Vivo Metric, Healdsburg, USA). EMG signals were amplified (×200) and band-pass filtered (10-1000 Hz). Both force and EMG signals were sampled using a 1401 interface (at 500 and 2000 Hz, respectively) and recorded on a computer equipped with Spike2 software (version 7.20, CED, Cambridge, UK).
Voluntary muscle activation, *i.e.* the extent to which the FDI muscle was activated by the CNS, was measured us-

ing the twitch interpolation technique (23, 29). In brief, supramaximal stimulation of the innervating nerve while the muscle is at rest activates all muscle fibres. The resultant force provides a measure of intrinsic muscle force (*i.e.* initial-doublet) (Fig. 2D). Stimulation applied during a voluntary contraction, however, only activates those muscle fibres which are not already activated by the CNS and the resulting force increment (*i.e.* superimposed twitch) provides a measure of voluntary muscle activation. Electrical stimulation of the ulnar nerve was applied using self-adhesive electrodes on the right wrist (pulse width 200μs; DS7A, Digitimer, Welwyn Garden City, UK). Stimulator output was set to 130% of the intensity required to evoke a maximal compound muscle action potential in the FDI muscle, and forces were evoked using double pulse stimulation (10 ms interval) to increase the signal-to-noise ratio (30).
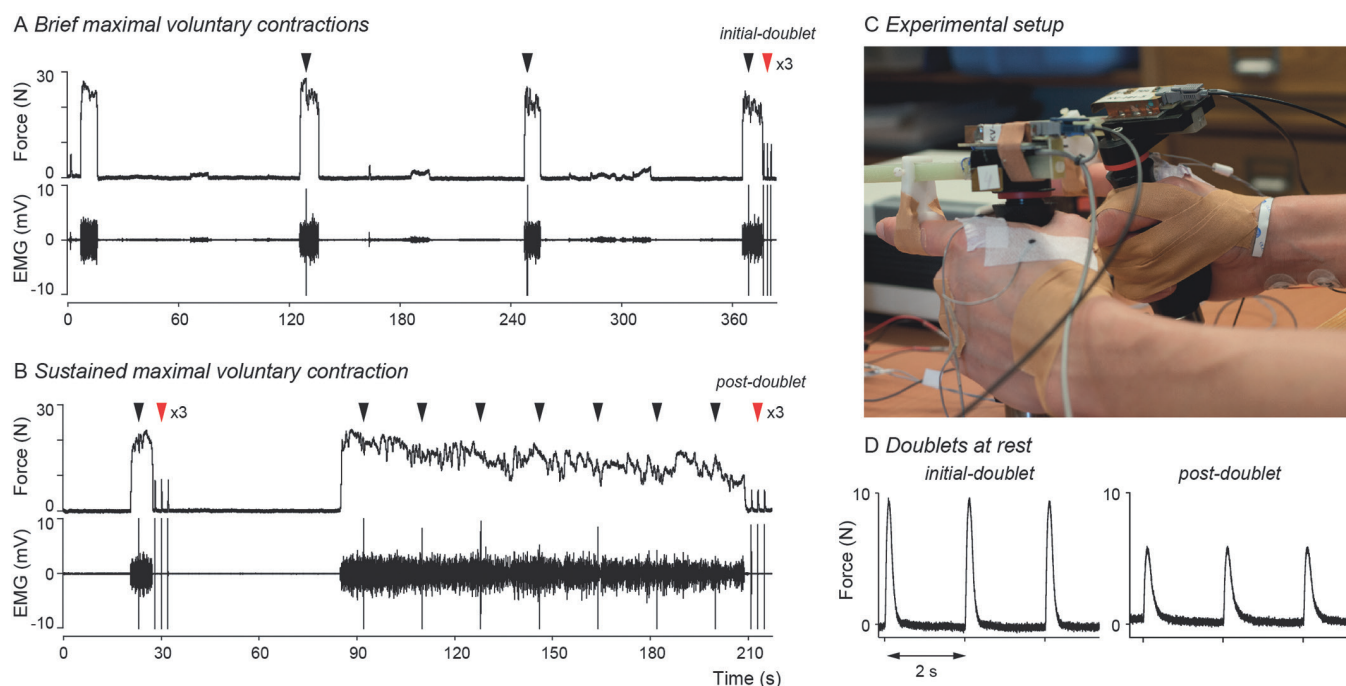
**Fig. 2.** Raw data and experimental setup.
Raw data from a pSS participant showing force and EMG of the right hand during the brief MVCs (**A**) and sustained MVC (**B**). Arrowheads indicate the timepoints of electrical stimulation (red arrowheads indicate 3 consecutive stimuli at rest, initial-doublet and post-doublet are labelled). (**C**) Photograph showing the experimental setup. (**D**) Evoked forces at rest (*i.e.* doublets). Note the decline in the post-doublet with respect to the initial-doublet. MVC: maximal voluntary contraction.

*Experimental tasks*
Participants performed three motor tasks (Fig. 2). Visual feedback of their force level and the task were displayed on a monitor in front of them, and experimenters provided vigorous verbal encouragement during maximal efforts.

*Task 1: Brief maximal voluntary contractions.* To obtain baseline measurements of maximal force, participants generated seven brief maximal voluntary contractions (MVCs, ~10s duration followed by 50s rest) alternating between hands (4 with the right hand). Voluntary muscle activation was measured during the last 2-3 contractions with the right hand. After the last contraction, three doublets were evoked at rest (2s interval) to provide a measure of intrinsic muscle force (*i.e.* initial-doublet).

*Task 2: Submaximal contractions.* Participants performed a series of submaximal contractions (at 10, 30, 50 and 70% MVC). This task provides additional information with respect to the relationship between voluntary force and voluntary muscle activation (full details provided as Appendix).

*Task 3: Sustained maximal voluntary contraction.* The final task was used to assess performance fatigability. Participants generated a brief MVC (~6s duration followed by 60s rest) followed by a sustained MVC (124s duration) with the right hand. Voluntary muscle activation was indexed during the brief MVC and at seven time points during the sustained MVC (18s interval). Three doublets evoked at rest after the brief MVC and after the sustained MVC (2s interval) assessed use-dependent changes in contractile function of the muscle (*i.e.* post-doublet).

***Modulators of self-reported fatigue***
Our second aim was to assess the relationship between self-reported fatigue and factors related to perceived fatigability (pain, depressed mood, anxiety, inflammatory biomarkers) and performance fatigability (force decline, voluntary muscle activation, post-doublet as assessed during Task 3) in pSS patients. Prior to the experimental session, self-reported fatigue was quantified using the Fatigue Severity Scale (FSS; 31) and Modified Fatigue Impact Scale (MFIS; 32) which distinguishes a physical and cognitive domain. A numerical rating scale (range 0-10) pain score was obtained from the ESSPRI (12) and symptoms of depressed mood and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS; 33).

Serum levels of IFN-γ, IL-1β, IL-6, and TNF-α were measured using a high-sensitivity immunoassay (MesoScale discovery, USA). Serum CXCL10 (IP-10) levels were measured using an ELISA, according to the manufacturer's protocol (Peprotech, USA). Myxovirus resistance protein 1 (MxA) levels were measured in lysed whole blood using an in-house EIA (34). The cut-off point for MxA positivity was defined at 100 ng/mL by calculating the mean and two standard deviations (SD) of healthy individuals (n=10). This value is similar to a previously reported cut-off (100 ng/mL, 35).

***Data and statistical analysis***
Force and EMG data were analysed using Spike2. EMG signals were transformed by calculating the root mean square (rms) over a moving window of 500 ms. MVC force was deter-

mined for the contractions during task 1 and 3. The amplitude of the initial- and post-doublets and superimposed twitches were measured, and voluntary muscle activation was calculated as (1 – superimposed twitch/initial-doublet) × 100%.

With regard to performance fatigability, three outcome measures were determined during Task 3. First, force decline during the sustained contraction was calculated as (1 – force during the last 6s/MVC) × 100%. Second, post-doublet was expressed as percentage of the initial-doublet to provide a measure of use-dependent changes in contractile function of the muscle fibres. Third, voluntary muscle activation during the sustained MVC was linearly corrected for the decline in contractile function (conform: (26, 36) and the mean value was calculated over the 7 time points to obtain a single value for each participant.

Statistical analysis was performed in RStudio (R version 3.6.1). Data are presented as number (percentage), mean (SD), or median (range) for categorical, normally distributed, and non-normally distributed data, respectively. Differences between pSS and controls were assessed using ANOVAs; sex was included as a covariate for MVC, doublets, and force decline to account for sex-related variance (37). Welch correction was used when variances between groups were unequal. Model residuals were inspected for normality using Q-Q plots and if required the dependent variable was transformed. If normality could not be achieved, Mann-Whitney U-test was used (HADS). $p$-values <0.05 were considered statistically significant.

Associations between self-reported fatigue (FSS, MFIS), performance fatigability (force decline, mean voluntary muscle activation, post-doublet) and perceived fatigability (HADS, ESSPRI-pain, inflammatory biomarkers) were explored using Pearson's and Spearman's correlation coefficients. Additionally, multivariable linear regression was used to explain the variance in self-reported fatigue scores using multiple explanatory variables (24, 26). Explanatory variables (with $p$<0.1 in univariable analysis) were included in a forward

stepwise model, and the more complex model survived if it explained significantly more variance than the simpler model.

## Results
Demographics of participants and clinical characteristics of patients are shown in Table I. For two pSS patients, physiological data were excluded from

the analyses due to a technical problem with the nerve stimulation. One control participant was excluded from the analysis of task 3 due to evident pacing during the task (*i.e.* not following task instructions). Serum levels of pro-inflammatory cytokines IFN-γ, IL-1β, IL-6, TNF-α and chemokine CXCL10 as well as whole blood MxA levels were available from 35 pSS patients.

**Table I.** Demographics and clinical characteristics.

|  | pSS (n=39) | Control (n=27) |
|---|---|---|
| **Demographics** | | |
| Age (years) | 49 (27-65) | 48 (27-68) |
| Females (n) | 34 (87.2%) | 22 (81.5%) |
| **Clinical characteristics** | | |
| Time since diagnosis (years) | 5 1-21) | |
| Symptom duration (years) | 11 (3-49) | |
| ESSDAI total | 3 (0-16) | |
| ESSDAI 0 | 8 (20.5%) | |
| ESSDAI 1-4 | 18 (46.2%) | |
| ESSDAI ≥5 | 13 (33.3%) | |
| ESSDAI subdomain activity (n) | | |
| Constitutional | 7 (17.9%) | |
| Lymphadenopathy | 1 (2.6%) | |
| Glandular | 12 (30.8%) | |
| Articular | 3 (7.7%) | |
| Cutaneous | 4 (10.3%) | |
| Pulmonary | 0 | |
| Renal | 0 | |
| Muscular | 0 | |
| Peripheral nervous system | 0 | |
| Central nervous system | 0 | |
| Haematological | 12 (30.8%) | |
| Biological | 27 (69.2%) | |
| Physician GDA | 5 (0-10) | |
| UWS flow, mL/min | 0.06 (0.00-0.31) | |
| Parotid or labial gland biopsy, FS ≥1 | 32 (94.1%) * | |
| Chisholm score | 4 (0-4) | |
| Schirmer (mean) mm/5min | 3.5 (0.0-21.5) | |
| OSS (mean) total score | 2 (0-10) | |
| **Serology** | | |
| Anti-SSA antibodies | 32 (82.1%) | |
| Anti-SSB antibodies | 19 (48.7%) | |
| IgG level, g/mL | 15.8 (7.8-44.1) | |
| RF level, IU/mL | 16 (0-170) | |
| **Patient-reported symptoms** | | |
| ESSPRI total score | 6 (1-9) | |
| ESSPRI dryness | 7 (2-9) | |
| ESSPRI physical fatigue | 7 (0-10) | |
| ESSPRI pain | 6 (0-9) | |
| **Handedness** | | |
| Edinburgh handedness inventory | 100 (-100-100) | 90 (40-100) |

Data are expressed as number of participants (%), mean (SD) or median (range). Schirmer's test (≤5mm/min and OSS ≥5) was considered positive if criteria were met in at least one eye. For Schirmer and OSS, the mean score of both eyes was calculated.
*Focus score and Chisholm score available from 34 patients.
ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; GDA: global disease activity; UWS: unstimulated whole saliva; FS: focus score; OSS: ocular staining score; RF: rheumatoid factor; FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale; HADS: Hospital Anxiety and Depression Scale.

**Table II.** Baseline physiological data and performance fatigability.

| | | pSS (n=37) | Control (n=27) | p-value | |
|---|---|---|---|---|---|
| | | | | Group | Sex |
| MVC left (N) | F | 33.4 (6.3) | 40.0 (9.9) | 0.003* | <0.001* |
| | M | 48.2 (7.5) | 49.6 (11.9) | | |
| MVC right (N) | F | 30.7 (7.2) | 31.9 (6.9) | 0.440 | 0.002* |
| | M | 39.2 (6.0) | 39.5 (9.7) | | |
| FDI $M_{max}$ amplitude (mV) | | 23.8 (6.2) | 25.3 (4.7) | 0.295 | - |
| Initial-doublet (N) | | 11.6 (3.1) | 10.6 (3.3) | 0.200 | 0.372 |
| Initial-doublet (%MVC) | F | 37.2 (6.4) | 33.3 (6.2) | 0.004* | 0.016* |
| | M | 34.0 (7.5) | 25.4 (7.0) | | |
| Voluntary muscle activation (%) | | 93.6 (57.5-99.1) | 96.4 (81.6-99.0) | 0.054 | - |
| Background force (%MVC) | | 92.6 (5.3) | 91.4 (5.2) | 0.369 | - |
| *Performance fatigability* | | | *(n=26)* | | |
| Force decline (%) | | 60.6 (9.4) | 63.1 (7.5) | 0.246 | 0.068 |
| Mean voluntary muscle activation (%) | | 81.5 (42.2-96.5) - | 87.8 (63.3-97.8) | 0.030* | |
| Post-doublet (%initial-doublet) | | 55.5 (19.7) | 46.8 (13.2) | 0.041* | - |

Data shown as mean (SD) or median (range).
MVC: maximal voluntary contraction; FDI: first dorsal interosseous muscle; $M_{max}$: maximal compound muscle action potential.

## Performance fatigability
### Similar maximal voluntary force at baseline
Table II shows the baseline measurements (task 1) of maximal voluntary force (MVC), electrically evoked force at rest (initial-doublet), and voluntary muscle activation. MVC force correlated with the initial-doublet (r=0.74, p<0.001) and voluntary muscle activation (r=0.38, p=0.002; log-transformed), indicating the relationship with intrinsic muscle force and CNS drive, respectively (all measured for the right hand). Although voluntary muscle activation showed a trend towards lower values in pSS (p=0.054, log-transformed) (Fig. 3A), MVC did not differ across groups (p=0.440). For the left hand, however, MVC was significantly weaker in pSS patients (mean: 35.3 vs. 41.8 N, p=0.003).

### Reduced voluntary muscle activation in pSS patients during the sustained MVC
Force decline during the sustained MVC is the resultant of changes in 1) voluntary muscle activation and 2) contractile function of the muscle fibres. The force decline did not dif-fer between pSS and controls (mean: 60.6 vs. 63.1%, p=0.246) (Table II and Fig. 3). However, voluntary muscle activation was lower in pSS patients (median: 81.5 vs. 87.8%, p=0.030, log-transformed).

The post-doublets showed a smaller decline in pSS compared to controls (mean: to 55.5 vs. 46.8% initial-doublet, p=0.041). Additionally, a negative association was found between the post-doublet and (log-transformed) mean voluntary muscle activation during the sustained MVC across both groups (r=-0.70, p<0.001) indicating a smaller decline in contractile function if voluntary muscle activation was lower (mainly pSS patients; see Discussion).

## Modulators of self-reported fatigue
### Higher levels of self-reported fatigue in pSS participants
Self-reported fatigue was significantly higher in pSS than controls (FSS mean: 4.4 vs. 2.6, p<0.001) (Table III). Twenty-six pSS patients (67%) but none of the controls scored above the cut-off for fatigue (FSS>4; 31). In pSS, mean scores on the MFIS were 17.0 (±8.1) for the physical domain and 14.9 (±8.0) for the cognitive domain.

### pSS patients reported higher levels of perceived fatigability
Patients reported higher levels of depressed mood (median: 3 vs. 0, p<0.001) and anxiety (5 vs. 4, p=0.026) than controls on the HADS (Table III). The median score of $ESSPRI_{pain}$ was 6 (range: 0–9) in pSS patients. The levels of inflammatory biomarkers in blood are provided in Table III.

### Self-reported fatigue in pSS was associated with performance and perceived fatigability
Correlations between self-reported fatigue, performance fatigability and modulators of perceived fatigability are shown in Table IV. Self-reported fatigue assessed with $MFIS_{physical}$ was associated with measures of performance fatigability: post-doublet, reflecting changes in contractile function following the sustained MVC, as well as (log-transformed) mean voluntary muscle activation during the sustained contraction (Fig. 4A).

Self-reported fatigue was also associated with modulators of perceived fatigability in pSS. $ESSPRI_{pain}$ was associated with both FSS and $MFIS_{physical}$ scores, $HADS_{anxiety}$ with FSS and $MFIS_{cognitive}$, whereas $HADS_{depression}$ was associated with all three fatigue assessments. With regard to inflammatory biomarkers, $MFIS_{cognitive}$ was negatively associated with IFN-$\gamma$ and TNF-$\alpha$ (Table IV). Both $MFIS_{cognitive}$ and $MFIS_{physical}$ were negatively associated with levels of MxA (rho=-0.49 and -0.37) and CXCL10 (rho=-0.37 and -0.36, respectively). Eleven out of 35 patients (31%) were MxA negative and reported higher levels of self-reported fatigue than MxA positive patients on the FSS (mean: 5.2 vs. 4.0), $MFIS_{physical}$ (24.8 vs. 13.9) and $MFIS_{cognitive}$ (18.0 vs. 12.2, all p<0.05). Interestingly, the two interferon-associated proteins were positively associated with systemic disease activity assessed with ESSDAI (MxA: r=0.45, p=0.007, CXCL10: rho=0.48, p=0.004).

Multivariable linear regression analysis was performed to determine factors which explain self-reported fatigue in pSS. Variance in $MFIS_{physical}$ scores was explained best by three predic-
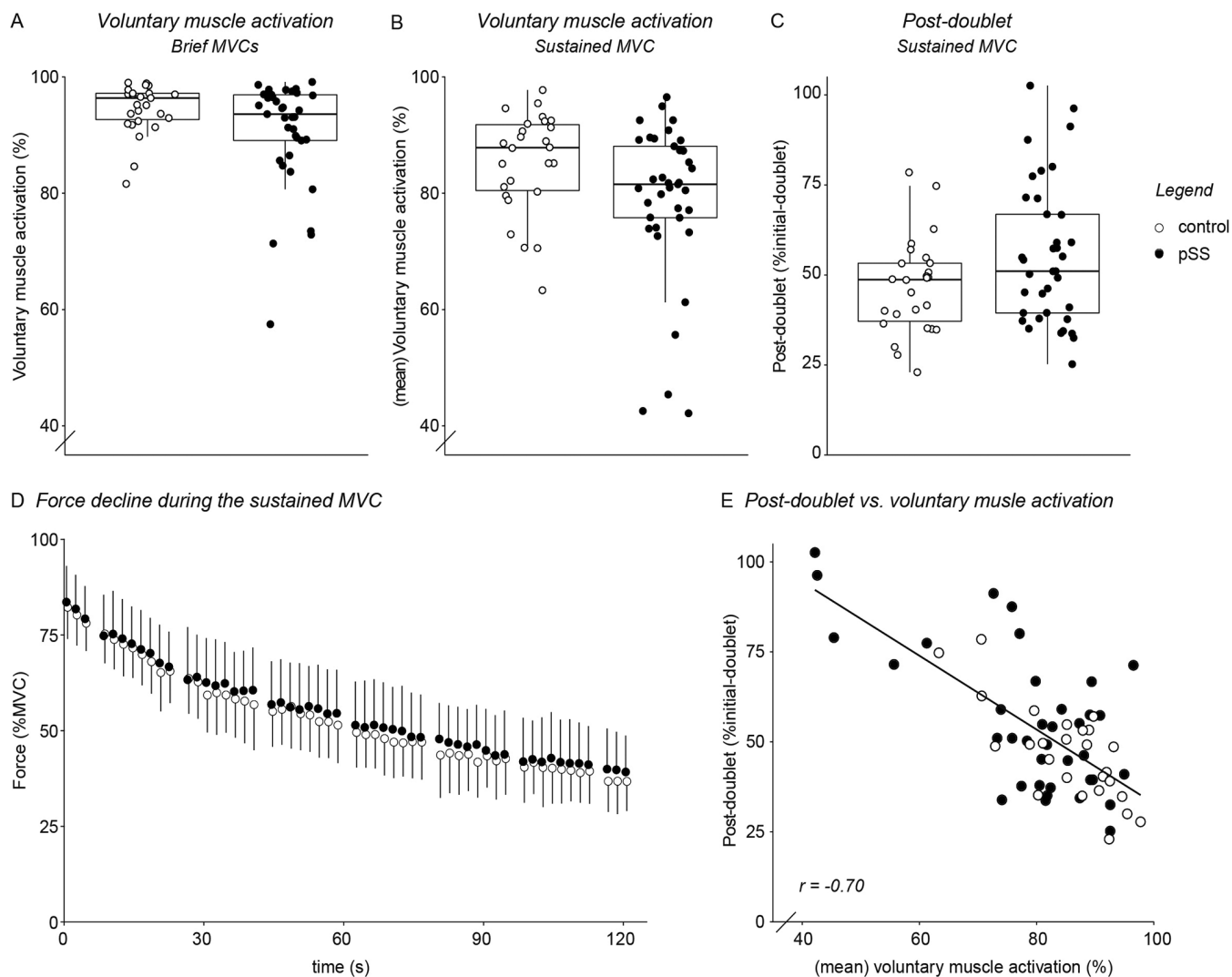
**Fig. 3.** Measures of performance fatigability.
Voluntary muscle activation (%) during the brief MVCs (**A**) and during the sustained MVC (**B**). (**C**) Post-doublet evoked after the sustained MVC. The box-plots in panels A-C indicate the median and 25th and 75th percentile. (**D**) Time-course of the force decline during the sustained MVC, mean value per group, error bars indicate standard deviations. (**E**) Relationship between voluntary muscle activation during the sustained MVC and the post-doublet following the sustained MVC. MVC: maximal voluntary contraction.

tors ($R^2=0.47$, $p<0.001$): HADS$_{depression}$, force decline, and ESSPRI$_{pain}$ (Fig. 4C). Inclusion of inflammatory biomarkers did not explain more variance. Both MFIS$_{cognitive}$ and FSS could be explained best by HADS$_{anxiety}$ ($R^2=0.39$, $p<0.001$ and $R^2=0.25$, $p=0.002$, respectively; all n=37). When adding (log-transformed) inflammatory biomarkers in blood, the MFIS$_{cognitive}$ model improved significantly with inclusion of IL-1β (from $R^2=0.18$ to $R^2=0.34$, $p=0.015$; n=35).

*Voluntary muscle activation was associated with pain and depressed mood*
Associations were also observed between mean voluntary muscle activa-

tion and modulators of perceived fatigability (ESSPRI$_{pain}$: rho=-0.34, $p=0.042$, HADS$_{depression}$: rho=-0.37, $p=0.024$). Lower levels of voluntary muscle activation during the sustained contraction were recorded in pSS participants reporting higher levels of pain or depression, indicating that performance fatigability and perceived fatigability may interact. Inflammatory biomarkers in blood were not associated with measures of performance fatigability.

**Discussion**
Fatigue is a major clinical symptom of pSS and the objective was to explore the basis of self-reported fatigue in pSS by assessing both performance fatiga-

bility during a sustained muscle contraction as well as factors modulating perceived fatigability. We observed that voluntary muscle activation was significantly lower in pSS patients during the sustained MVC, indicating that task performance was impeded by a reduced capacity of the CNS to sustain optimal drive to the muscle. Furthermore, self-reported fatigue in pSS was associated with parameters relating to performance fatigability (decline in both voluntary muscle activation and contractile function) as well as perceived fatigability (including symptoms of pain, depression, and anxiety). Finally, in the case of the MFIS$_{physical}$ questionnaire a greater amount of variance in self-reported

**Table III.** Self-reported fatigue and modulators of perceived fatigability.

|  | pSS (n=39) | | Control (n=27) | |
|---|---|---|---|---|
| **Self-reported fatigue** | | | | |
| FSS | 4.4 | (1.3) | 2.6 | (0.7) |
| FSS >4 | 26 | (66.7%) | 0 | (0%) |
| MFIS total | 35.1 | (15.6) | - | |
| MFIS$_{physical}$ | 17.0 | (8.1) | - | |
| MFIS$_{cognitive}$ | 14.9 | (8.0) | - | |
| **Perceived fatigability** | | | | |
| HADS depression | 3 | (0-12) | 0 | (0-7) |
| HADS Anxiety | 5 | (1-13) | 4 | (0-8) |
| ESSPRI pain | 6 | (0-9) | - | |
| **Inflammatory biomarkers** | **(n=35)** | | | |
| IFN-$\gamma$ (pg/mL) | 5.54 | (2.00-18.92) | - | |
| IL-1$\beta$ (pg/mL) | 0.05 | (0.01-0.28) | - | |
| IL-6 (pg/mL) | 0.57 | (0.19-17.68) | - | |
| TNF-$\alpha$ (pg/mL) | 1.54 | (0.64-3.52) | - | |
| CXCL10 (pg/mL) | 160 | (29-1000) | - | |
| MxA (ng/mL) | 153.8 | (10.0-913.7) | - | |
| MxA > 100 ng/mL | 11 | (31.4%) | - | |

Data shown as mean (SD) or median (range).

fatigue could be explained by combining factors relating to both perceived- and performance fatigability.

*pSS patients had lower levels of voluntary muscle activation*
Patients showed significantly lower levels of voluntary muscle activation during the sustained MVC than controls, but there was no difference in the amount of force decline. In pSS, the CNS has difficulties maintaining an optimal drive to the muscles which results in an attenuated use-dependent decline in contractile function of the muscle fibres (23). This is demonstrated by a smaller decline in the post-doublet in pSS and by the negative correlation between post-doublet and mean voluntary muscle activation. The larger decline in CNS drive in pSS patients is similar to what has previously been observed in another autoimmune disease, multiple sclerosis (26). In summary, performance fatigability reflects changes in CNS drive and recording of voluntary muscle activation provides valuable insight with regards to the underlying mechanisms.

A limitation of the twitch interpolation technique, which was used to detect differences in voluntary muscle activation between pSS and controls, is that electrical stimulation of a peripheral nerve does not provide insight into where in the nervous system the output failure developed (23, 38). In pSS, neuropathy could play a role in the decreased muscle activation since ~11% of patients have this disease manifestation (39, 40), though this percentage may even be an underestimation (41). Nevertheless, the maximal compound muscle action potential of the FDI muscle was conserved in pSS participants (Table II, FDI M$_{max}$) suggesting that motor neuropathy was unlikely. Involvement of the CNS has also been reported in pSS but is relatively rare (<4% of patients) (39, 40) and (known) neurologic involvement was an exclusion criterion in our study.

A more likely explanation for the lower levels of voluntary muscle activation in

**Table IV.** Correlations between self-reported fatigue and modulators of performance- and perceived fatigability in pSS participants.

|  |  | FSS | | MFIS$_{physical}$ | | MFIS$_{cognitive}$ | |
|---|---|---|---|---|---|---|---|
|  |  | corr. | p-value | corr. | *p*-value | corr. | *p*-value |
| **Performance fatigability (n=37)** | | | | | | | |
| Force decline (%MVC) | r | 0.08 | 0.643 | -0.17 | 0.322 | 0.08 | 0.649 |
| Mean voluntary muscle activation[†] (%) | r | -0.13 | 0.432 | -0.37 | 0.026* | -0.10 | 0.546 |
| Post-doublet (%) | r | 0.06 | 0.726 | 0.43 | 0.008* | 0.12 | 0.479 |
| **Perceived fatigability (symptoms, n=39)** | | | | | | | |
| ESSPRI pain | rho | 0.33 | 0.040* | 0.51 | 0.001* | 0.30 | 0.067 |
| HADS depression | rho | 0.45 | 0.004* | 0.45 | 0.004* | 0.52 | <0.001* |
| HADS anxiety | rho | 0.40 | 0.012* | 0.29 | 0.070 | 0.57 | <0.001* |
| **Perceived fatigability (biomarkers, n=35)** | | | | | | | |
| IFN-$\gamma$ (pg/mL) | rho | -0.18 | 0.308 | -0.12 | 0.494 | -0.36 | 0.035* |
| IL-1$\beta$ (pg/mL) | rho | -0.09 | 0.626 | -0.22 | 0.224 | -0.34 | 0.057 |
| IL-6 (pg/mL) | rho | 0.00 | 0.983 | -0.04 | 0.835 | -0.33 | 0.052 |
| TNF-$\alpha$ (pg/mL) | rho | -0.04 | 0.807 | -0.29 | 0.089 | -0.36 | 0.032* |
| MxA (ng/mL) | rho | -0.17 | 0.332 | -0.49 | 0.003* | -0.37 | 0.029* |
| CXCL10 (pg/mL) | rho | -0.25 | 0.144 | -0.37 | 0.028* | -0.36 | 0.033* |

[†] Log-transformed.

A *Self-reported fatigue vs. post-doublet and voluntary muscle activation*
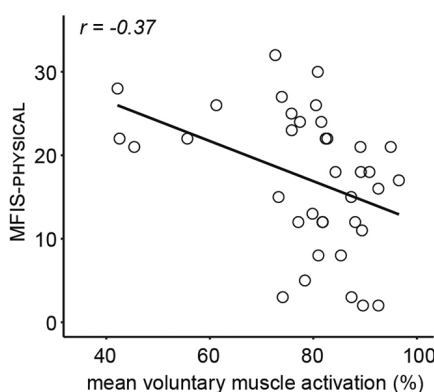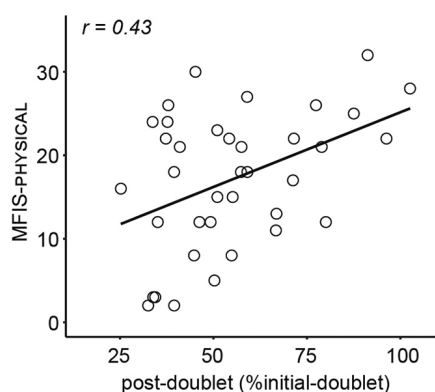
B *Voluntary muscle activation vs. pain*
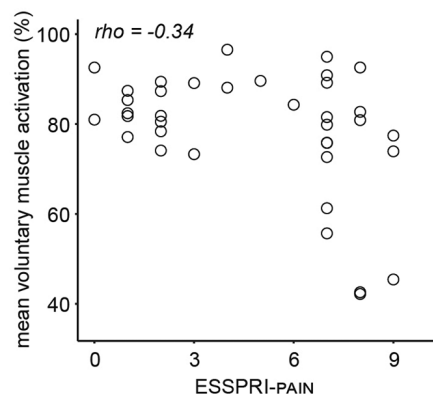


C *Self-reported fatigue: multivariable linear regression*

*MFIS-PHYSICAL*
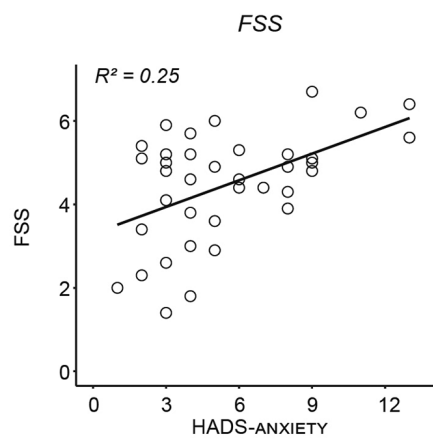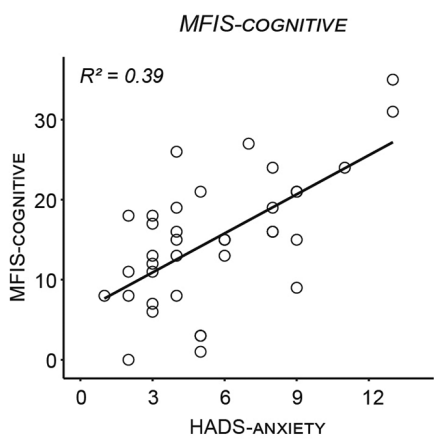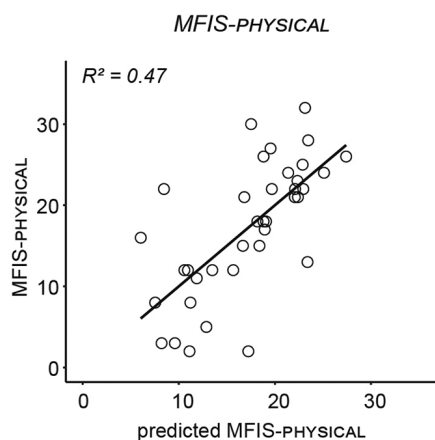


| Predictor | standardised β | p-value |
|---|---|---|
| HADS-DEPRESSION | 0.35 | 0.017 |
| ESSPRI-PAIN | 0.48 | 0.001 |
| Force decline | -0.31 | 0.025 |

*MFIS-COGNITIVE*

| Predictor | standardised β | p-value |
|---|---|---|
| HADS-ANXIETY | 0.63 | <0.001 |

*FSS*

| Predictor | standardised β | p-value |
|---|---|---|
| HADS-ANXIETY | 0.50 | 0.002 |

**Fig. 4.** Self-reported fatigue and measures of performance- and perceived fatigability.
**(A)** Relationships between performance fatigability (post-doublet, mean voluntary muscle activation) and the MFIS$_{physical}$ score. **(B)** Relationship between ESSPRI$_{pain}$ score and mean voluntary muscle activation. **(C)** Multivariable linear regression models for self-reported fatigue. For the MFIS$_{physical}$, a predicted score based on the regression model is plotted along the x-axis. MFIS$_{cognitive}$ and FSS were best explained by HADS$_{anxiety}$.
MFIS: Modified Fatigue Impact Scale; FSS: Fatigue Severity Scale; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; HADS: Hospital Anxiety and Depression Scale.

pSS is that the CNS drive was influenced by factors related to perceived fatigability (38) (Fig. 1). Indeed, we observed associations of voluntary muscle activation with pain and depression scores. Pain can be regarded as a homeostatic dysfunction (42), and the perception of pain could affect voluntary motor output via central pathways. Several studies have shown reduced maximal force after experimentally induced pain; some also showed reductions in voluntary muscle activation (43) though others found no changes (44). Lower levels of voluntary muscle activation have also been described in fibromyalgia (45); a condition

which is characterised by generalised pain. However, in another study voluntary muscle activation during a fatiguing motor task was not reduced in fibromyalgia patients (22).

*pSS fatigue is associated with measures of performance and perceived fatigability*
In the present study, two-thirds of pSS patients scored high on the fatigue questionnaires, which is in line with previous findings (5, 6, 46). With regard to perceived fatigability, our study confirmed the previously reported associations between self-reported fa-

tigue and symptoms of pain, depression, and anxiety in pSS (5, 19, 47-51). As new finding, we showed that pain and depression can negatively affect the CNS output resulting in a decline in motor performance.
Negative associations with fatigue were observed for several inflammatory biomarkers. In particular, the two interferon-associated proteins (MxA and CXCL10) were negatively associated with both subscales of the MFIS. These findings confirm earlier data that proinflammatory cytokine levels, as well as markers of interferon activity, show negative associations with self-reported

fatigue in pSS (19, 20, 52, 53). It should be noted, however, that not all studies found such associations (47, 54, 55), possibly owing to differences between cohorts and the selection of biomarkers. The negative associations between inflammatory biomarkers and fatigue seem counterintuitive. Firstly, we observed a positive association of the inflammatory biomarkers with systemic disease activity (ESSDAI). Moreover, there is some evidence to suggest that IFN-α induces fatigue, since administration of recombinant cytokines in cancer patients resulted in a significant increase in symptoms of fatigue (56). Howard-Tripp and colleagues (2016) postulated that chronic inflammation may lead to an exaggerated anti-inflammatory response that could promote 'sickness behaviour' including fatigue; the negative association between pro-inflammatory cytokines and fatigue could therefore reflect a disbalanced immune system.

Finally, for the MFIS$_{physical}$ questionnaire, almost half the variance in self-reported fatigue could be explained by accounting for the force decline during the sustained MVC (a measure of performance fatigability) as well as symptoms of pain and depression (both measures of perceived fatigability), indicating that both attributes of the fatigue framework (3, 14) (Fig. 1) are involved in pSS-related fatigue. Inflammatory biomarkers in blood did not help to explain more variance in this model.

## Conclusion

In conclusion, this study demonstrates that performance in pSS, assessed during a sustained MVC of a hand muscle, was limited by a reduced capacity of the CNS to sustain output to the muscle. Furthermore, we identified a relationship between self-reported fatigue and objective decline in performance in pSS. These findings indicate that performance fatigability should be considered when investigating fatigue. Moreover, we have shown that self-reported fatigue in pSS is a multifactorial symptom through associations with both performance fatigability (force decline) and perceived fatigability (pain and depressed mood). Though

the immune system may potentially modulate fatigue, further research is warranted to unravel the underlying mechanism.

## Acknowledgement

## References

1. KORTE SM, STRAUB RH: Fatigue in inflammatory rheumatic disorders: Pathophysiological mechanisms. *Rheumatology* (Oxford) 2019; 58: V35-50. https://doi.org/10.1093/rheumatology/kez413
2. DANTZER R, HEIJNEN CJ, KAVELAARS A, LAYE S, CAPURON L: The neuroimmune basis of fatigue. *Trends Neurosci* 2014; 37(1): 39-46. https://doi.org/10.1016/j.tins.2013.10.003
3. KLUGER BM, KRUPP LB, ENOKA RM: Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 2013; 80: 409-16. https://doi.org/10.1212/wnl.0b013e31827f07be
4. VIVINO FB: Sjögren's syndrome: Clinical aspects. Clin Immunol 2017; 182: 48-54. https://doi.org/10.1016/j.clim.2017.04.005
5. SEGAL B, THOMAS W, ROGERS T *et al.*: Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. *Arthritis Care Res* 2008; 59: 1780-7. https://doi.org/10.1002/art.24311
6. ARENDS S, MEINERS PM, MOERMAN RV *et al.*: Physical fatigue characterises patient experience of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2017; 35: 255-61.
7. NG WF, BOWMAN SJ: Primary Sjögren's syndrome: too dry and too tired. *Rheumatology* (Oxford) 2010; 49: 844-53. https://doi.org/10.1093/rheumatology/keq009
8. OMDAL R, MELLGREN SI, NORHEIM KB: Pain and fatigue in primary Sjögren's syndrome. *Rheumatology* 2021; 60: 3099-106. https://doi.org/10.1093/rheumatology/kez027
9. MENGSHOEL AM, NORHEIM KB, OMDAL R: Primary Sjögren's syndrome: Fatigue is an ever-present, fluctuating, and uncontrollable lack of energy. *Arthritis Care Res* 2014; 66: 1227-32. https://doi.org/10.1002/acr.22263
10. SEGAL B, BOWMAN SJ, FOX PC *et al.*: Primary Sjögren's syndrome: health experiences and predictors of health quality among patients in the United States. *Health Qual Life Outcomes* 2009; 7: 1-9. https://doi.org/10.1186/1477-7525-7-46
11. MEIJER JM, MEINERS PM, SLATER JJRH *et al.*: Health-related quality of life, employment and disability in patients with Sjögren's syndrome. *Rheumatology* 2009; 48: 1077-82. https://doi.org/10.1093/rheumatology/kep141
12. SEROR R, RAVAUD P, MARIETTE X *et al.*: EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): Development of a consensus patient index for primary Sjögren's

syndrome. *Ann Rheum Dis* 2011; 70: 968-72. https://doi.org/10.1136/ard.2010.143743
13. BOWMAN SJ, EVERETT CC, O'DWYER JL *et al.*: Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's syndrome. *Arthritis Rheumatol* 2017; 69: 1440-50. https://doi.org/10.1002/art.40093
14. ENOKA RM, DUCHATEAU J: Translating fatigue to human performance. *Med Sci Sports Exerc* 2016; 48: 2228-38. https://doi.org/10.1249/mss.0000000000000929
15. ENOKA RM, ALMUKLASS AM, ALENAZY M, ALVAREZ E, DUCHATEAU J: Distinguishing between fatigue and fatigability in multiple sclerosis. *Neurorehabil Neural Repair* 2021; 35: 960-73. https://doi.org/10.1177/15459683211046257
16. ZIJDEWIND I, PRAK RF, WOLKORTE R: Fatigue and fatigability in persons with multiple sclerosis. *Exerc Sport Sci Rev* 2016; 44: 123-8. https://doi.org/10.1249/jes.0000000000000088
17. SEAMON BA, HARRIS-LOVE MO: Clinical assessment of fatigability in multiple sclerosis: a shift from perception to performance. *Front Neurol* 2017; 7: 194. https://doi.org/10.3389/fneur.2016.00194
18. MARRELLI K, CHENG AJ, BROPHY JD, POWER GA: Perceived versus performance fatigability in patients with rheumatoid arthritis. *Front Physiol* 2018; 9: 1395. https://doi.org/10.3389/fphys.2018.01395
19. DAVIES K, MIRZA K, TARN J *et al.*: Fatigue in primary Sjögren's syndrome (pSS) is associated with lower levels of proinflammatory cytokines: a validation study. *Rheumatol Int* 2019; 39: 1867-73. https://doi.org/10.1007/s00296-019-04354-0
20. BODEWES ILA, SPEK PJV, LEON LG *et al.*: Fatigue in Sjögren's syndrome: A search for biomarkers and treatment targets. *Front Immunol* 2019; 10: 312. https://doi.org/10.3389/fimmu.2019.00312
21. MÆLAND E, MIYAMOTO ST, HAMMENFORS D, VALIM V, JONSSON MV: Understanding fatigue in Sjögren's syndrome: outcome measures, biomarkers and possible interventions. *Front Immunol* 2021; 12: 703079. https://doi.org/10.3389/fimmu.2021.703079
22. BACHASSON D, GUINOT M, WUYAM B *et al.*: Neuromuscular fatigue and exercise capacity in fibromyalgia syndrome. *Arthritis Care Res* (Hoboken) 2013; 65: 432-40. https://doi.org/10.1002/acr.21845
23. GANDEVIA SC: Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 2001; 81: 1725-89. https://doi.org/10.1152/physrev.2001.81.4.1725
24. WOLKORTE R, HEERSEMA DJ, ZIJDEWIND I: Muscle fatigability during a sustained index finger abduction and depression scores are associated with perceived fatigue in patients with relapsing-remitting multiple sclerosis. *Neurorehabil Neural Repair* 2015; 29: 796-802. https://doi.org/10.1177/1545968314567151
25. World Medical Association: World Medical Association Declaration of Helsinki. *JAMA* 2013; 310: 2191-4. https://doi.org/10.1001/jama.2013.281053
26. STEENS A, DE VRIES A, HEMMEN J *et al.*: Fatigue perceived by multiple sclerosis pa-

tients is associated with muscle fatigue. *Neurorehabil Neural Repair* 2012; 26: 48-57. https://doi.org/10.1177/1545968311416991

27. PRAK RF, VAN DER NAALT J, ZIJDEWIND I: Self-reported fatigue after mild traumatic brain injury is not associated with performance fatigability during a sustained maximal contraction. *Front Physiol* 2019; 9: 1919. https://doi.org/10.3389/fphys.2018.01919

28. VAN DUINEN H, POST M, VAARTJES K *et al*.: MR compatible strain gauge based force transducer. *J Neurosci Methods* 2007; 164: 247-54. https://doi.org/10.1016/j.jneumeth.2007.05.005

29. MERTON PA: Voluntary strength and fatigue. *J Physiol* 1954; 123: 553-64. https://doi.org/10.1113/jphysiol.1954.sp005070

30. GANDEVIA SC, MCKENZIE DK: Activation of human muscles at short muscle lengths during maximal static efforts. *J Physiol* 1988; 407: 599-613. https://doi.org/10.1113/jphysiol.1988.sp017434

31. KRUPP LB, LAROCCA NG, MUIR-NASH J, STEINBERG AD: The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46: 1121-3. https://doi.org/10.1001/archneur.1989.00520460115022

32. Multiple Sclerosis Council for Clinical Practice Guidelines: Fatigue and Multiple Sclerosis: Evidence Based Management Strategies for Fatigue in Multiple Sclerosis. Washington D.C., Paralyzed Veterans of America; 1998.

33. ZIGMOND AS, SNAITH RP: The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361-70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

34. VERSTAPPEN GM, GAO L, PRINGLE S *et al*.: The transcriptome of paired major and minor salivary gland tissue in patients with primary Sjögren's syndrome. *Front Immunol* 2021; 12. https://doi.org/10.3389/fimmu.2021.681941

35. MARIA NI, BRKIC Z, WARIS M *et al*.: MxA as a clinically applicable biomarker for identifying systemic interferon type i in primary Sjögren's syndrome. *Ann Rheum Dis* 2014; 73(6): 1052-9. https://doi.org/10.1136/annrheumdis-2012-202552

36. SCHILLINGS ML, HOEFSLOOT W, STEGEMAN DF, ZWARTS MJ: Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. *Eur J Appl Physiol* 2003; 90: 562-8. https://doi.org/10.1007/s00421-003-0913-4

37. SARS V, PRAK RF, HORTOBÁGYI T, ZIJDEWIND I: Age- and sex-related differences in motor performance during sustained maximal voluntary contraction of the first dorsal

interosseous. *Front Physiol* 2018; 9: 637. https://doi.org/10.3389/fphys.2018.00637

38. TAYLOR JL, AMANN M, DUCHATEAU J, MEEUSEN R, RICE CL: Neural contributions to muscle fatigue: from the brain to the muscle and back again. *Med Sci Sports Exerc* 2016; 48: 2294-306. https://doi.org/10.1249/mss.0000000000000923

39. RAMOS-CASALS M, SOLANS R, ROSAS J *et al*.: Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine* (Baltimore). 2008; 87: 210-9. https://doi.org/10.1097/md.0b013e318181e6af

40. SEROR R, THEANDER E, BRUN JG *et al*.: Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and Patient indexes (ESSPRI). *Ann Rheum Dis* 2015; 74: 859-66. https://doi.org/10.1136/annrheumdis-2013-204615

41. GØRANSSON LG, HERIGSTAD A, TJENSVOLL AB, HARBOE E, MELLGREN SI, OMDAL R: Peripheral neuropathy in primary Sjögren syndrome. *Arch Neurol* 2006; 63: 1612-5. https://doi.org/10.1001/archneur.63.11.1612

42. CRAIG ADB: Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* 2003; 26: 1-30. https://doi.org/10.1146/annurev.neuro.26.041002.131022

43. KENNEDY DS, MCNEIL CJ, GANDEVIA SC, TAYLOR JL: Firing of antagonist small-diameter muscle afferents reduces voluntary activation and torque of elbow flexors. *J Physiol* 2013; 591: 3591-604. https://doi.org/10.1113/jphysiol.2012.248559

44. KHAN SI, MCNEIL CJ, GANDEVIA SC, TAYLOR JL: Effect of experimental muscle pain on maximal voluntary activation of human biceps brachii muscle. *J Appl Physiol* 2011; 111: 743-50. https://doi.org/10.1152/japplphysiol.00603.2011

45. NØRREGAARD J, BÜLOW PM, VESTERGAARD-POULSEN P, THOMSEN C, DANNESKIOLD-SAMØE B: Muscle strength, voluntary activation and cross-sectional muscle area in patients with fibromyalgia. *Br J Rheumatol* 1995; 34: 925-31. https://doi.org/10.1093/rheumatology/34.10.925

46. HALDORSEN K, BJELLAND I, BOLSTAD AI, JONSSON R, BRUN JG: A five-year prospective study of fatigue in primary Sjögren's syndrome. *Arthritis Res Ther* 2011; 13: R167. https://doi.org/10.1186/ar3487

47. KARAGEORGAS T, FRAGIOUDAKI S, NEZOS A, KARAISKOS D, MOUTSOPOULOS HM, MAVRAGANI CP: Fatigue in primary Sjögren's syndrome: clinical, laboratory, psychometric, and biologic associations. *Arthritis Care*

*Res* 2016; 68: 123-31. https://doi.org/10.1002/acr.22720

48. STRÖMBECK B, EKDAHL C, MANTHORPE R, JACOBSSON LTH: Physical capacity in women with primary Sjögren's syndrome: A controlled study. *Arthritis Care Res* (Hoboken) 2003; 49: 681-8. https://doi.org/10.1002/art.11384

49. DASSOUKI T, BENATTI FB, PINTO AJ *et al*.: Objectively measured physical activity and its influence on physical capacity and clinical parameters in patients with primary Sjögren's syndrome. *Lupus* 2017; 26: 690-7. https://doi.org/10.1177/0961203316674819

50. KOH JH, KWOK SK, LEE J *et al*.: Pain, xerostomia, and younger age are major determinants of fatigue in Korean patients with primary Sjögren's syndrome: a cohort study. *Scand J Rheumatol* 2017; 46: 49-55. https://doi.org/10.3109/03009742.2016.1153142

51. HUANG T, LI Y, LUO Y, ZHOU Y, ZHAO Y, LIU Y: Research progress on the pathogenesis and quality of life of patients with primary Sjögren's syndrome complicated by depression. *Clin Exp Rheumatol* 2022; 40: 647-54. https://doi.org/10.55563/clinexprheumatol/nspi47

52. HOWARD-TRIPP N, TARN J, NATASARI A *et al*.: Fatigue in primary Sjögren's syndrome is associated with lower levels of proinflammatory cytokines. *RMD Open* 2016; 2. https://doi.org/10.1136/rmdopen-2016-000282

53. D'ELIA HF, BJURMAN C, REHNBERG E, KVIST G, KONTTINEN YT: Interleukin 6 and its soluble receptor in a central role at the neuroimmunoendocrine interface in Sjögren syndrome: An explanatory interventional study. *Ann Rheum Dis* 2009; 68: 285-6. https://doi.org/10.1136/ard.2008.091256

54. HARTKAMP A, GEENEN R, BIJL M, KRUIZE AA, GEDAERT GLR, DERKSEN RHWM: Serum cytokine related to multiple dimensions of fatigue in patients with primary Sjögren's syndrome. *Ann Rheum Dis* 2004; 63: 1335-7. https://doi.org/10.1136/ard.2003.011825

55. BODEWES ILA, AL-ALI S, VAN HELDEN-MEEUWSEN CG *et al*.: Systemic interferon type I and type II signatures in primary Sjögren's syndrome reveal differences in biological disease activity. *Rheumatology* (Oxford) 2018; 57): 921-30. https://doi.org/10.1093/rheumatology/kex490

56. CAPURON L, GUMNICK JF, MUSSELMAN DL *et al*.: Neurobehavioral effects of interferon-α in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 2002; 26: 643-52. https://doi.org/10.1016/s0893-133x(01)00407-9