FATIGUE IN SJÖGREN'S

A burden to patients and the society
a challenge for clinicians and scientists

Wan-Fai Ng

Professor of Rheumatology, Newcastle university, UK

Honorary Consultant Rheumatologist, Newcastle upon Tyne NHS Foundation Trust, UK

Director, NIHR Newcastle Clinical Research Facility, UK

Deputy Musculoskeletal Theme Lead, NIHR Newcastle Biomedical Research Centre, UK

Chief Investigator, UK primary Sjögren's syndrome registry

Trustee, British Sjögren's Syndrome Association

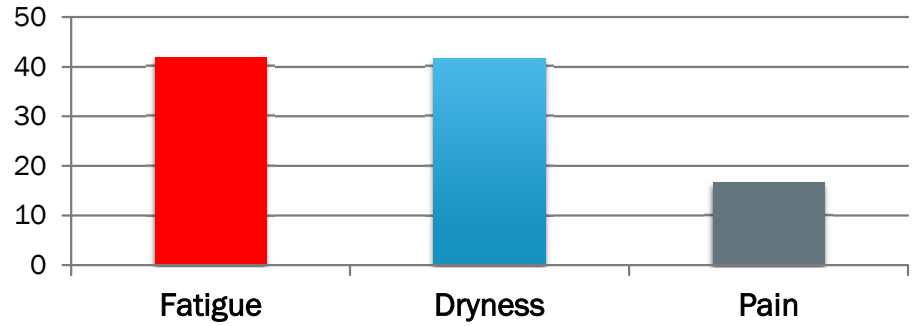
Medical Board Member, Sjögren's Europe

Newcastle University

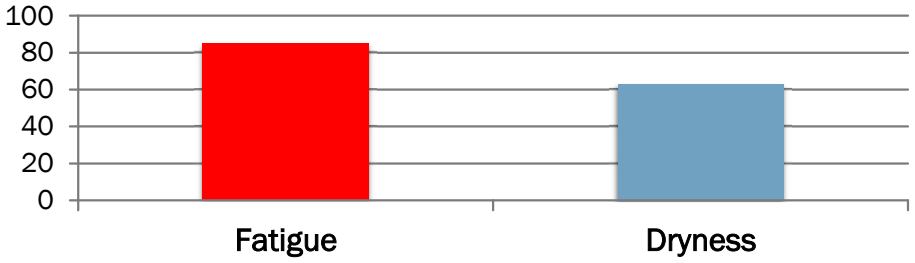
Fatigue is common among people with Sjögren's syndrome

- ***Fatigue affects ~70% of people with Sjögren's syndrome***
- ***Over 40% of people with Sjögren's syndrome rated fatigue being the most important symptom needing improvement***
- ***Some people with Sjögren's syndrome do not experience significant fatigue***

Symptom most in need of improvement

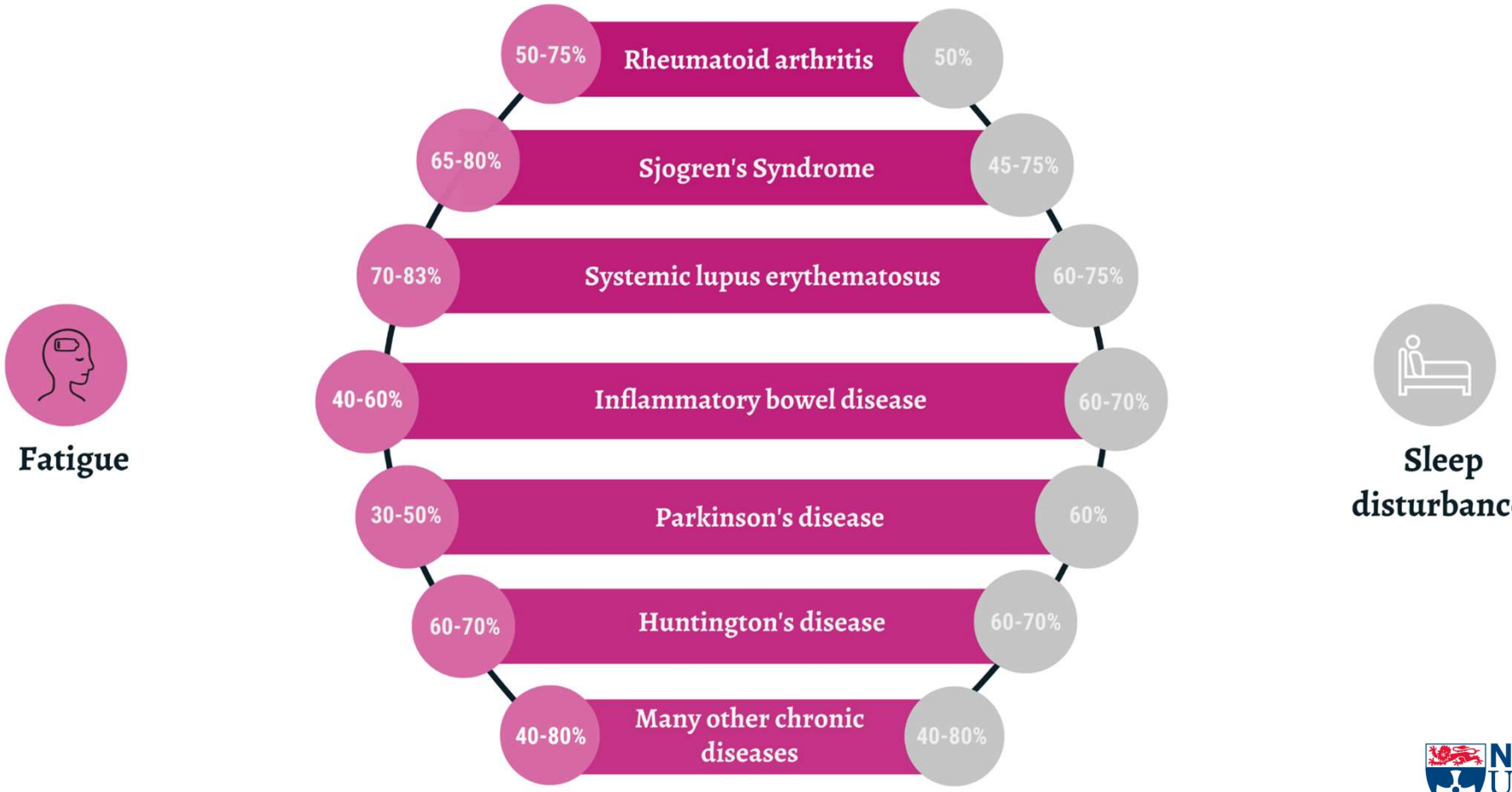


Symptom most or second most in need of improvement



N = 843 (AECG)
37 UK centres

Fatigue is a common feature in many chronic disease



Newcastle University

Fatigue is a huge burden to patients and the society

Patient's perspective

- Among the most disabling symptoms needful of treatment
- Often among the first symptoms patients notice
- In IMID, fatigue persists even when in clinical remission
- Should be included among the Core Outcome measures

Associated with

- Impaired activities of daily living performance
- Sickness absence and job loss in IMIDs
- Poor health-related quality of life in IMIDs and PD
- Increased mortality and risk of several complex disorders and death

Increased societal and healthcare costs

- Sickness absence
- Job loss
- Disability claims
- Increased medical consultations

Newcastle University

Why aren’t we do more about fatigue?

What is fatigue?

What causes fatigue?

How to measure fatigue?

How to treat fatigue?

Newcastle University

WHAT IS FATIGUE?

- Most (if not all) people would have had experience that we called “fatigue” or “tiredness”
- Is it the same fatigue that patients go to see their doctor for?
- Qualitative research studies typically suggest that the patients’ experience is ***different from their “usual” fatigue***
  - *More profound and prolonged*
  - *Unpredictable*
  - *Persists after rest*

Newcastle University

WHAT IS FATIGUE?

- ARE THERE DIFFERENT “TYPES” OF FATIGUE?

- Is fatigue the same across diseases or is it disease-specific?
- What about different “types” of fatigue such as “physical”, “mental”, “central”, “peripheral”, etc.? Are they truly distinct phenomena or are they different facets of the same phenomenon?

Newcastle University

WHAT IS FATIGUE (in research)?

- No consensus definition
- Essentially defined by the fatigue measurement tool used in a particular research
- Even when the same tool is used, the “cut-off value” for defining fatigue varies between studies

Newcastle University

WHAT IS FATIGUE?

- A multi-dimensional phenomenon in which the **biophysiological, cognitive, motivational** and **emotional state** of the body is affected resulting in ***significant impairment*** of the individual's ***ability to function*** in their normal capacity"

Newcastle University

WHAT “CAUSE” FATIGUE AND HOW TO MANAGE FATIGUE

SICKNESS BEHAVIOUR

- The constellation of non-specific symptoms of sickness such as ***weakness***, ***malaise***, ***fatigue***, ***aches***, ***inability to concentrate*** and somewhat ***depressed*** and ***lethargic***, is collectively referred to as “sickness behaviour”

(Benjamin Hart, 1988)

Newcastle University

SICKNESS BEHAVIOUR

- A highly organized strategy of the body to fight infections
- In humans, metabolic rate needs to be increased by 13% to raise 1 °C in body temperature.
- Also motivational interpretation of sickness behaviour

Newcastle University

(Benjamin Hart, 1988)

“INDIRECT” EFFECTS OF INFLAMMATION

- Disrupts ***circadian rhythms*** (vice versa)
- Leads to ***sleep disturbances*** (e.g. reduced slow wave sleep, increase REM, subjective sleep “quality”)
- Increases ***oxidative stress***
- May induce “***depression-like***” symptoms
- Chronic exposure to inflammatory cytokines blunts ***Hypothalamus-Pituitary-Adrenal (HPA)*** responses

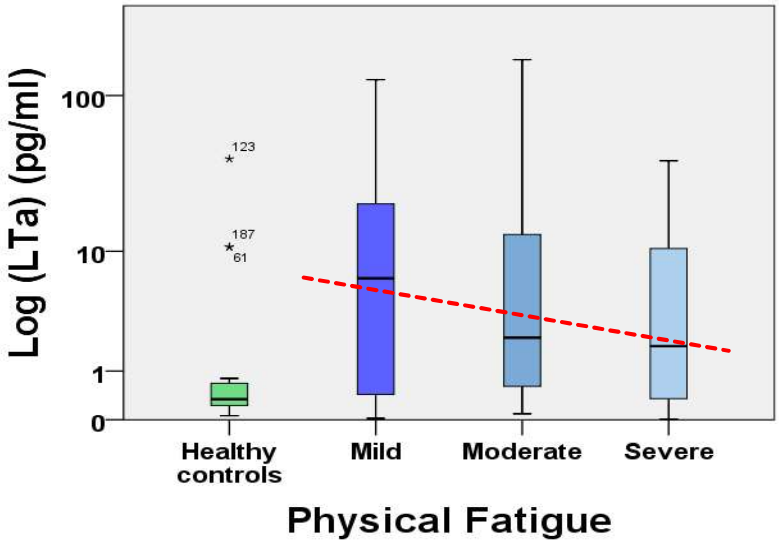
Newcastle University

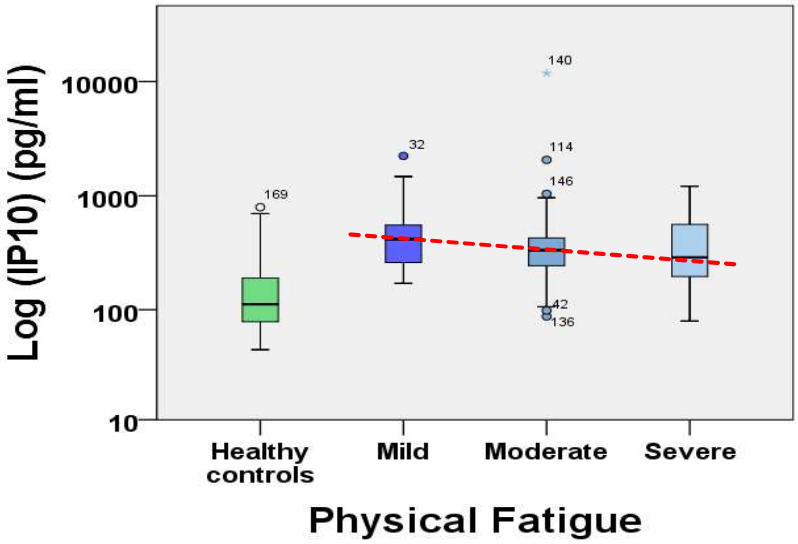
Inflammation and fatigue in chronic immune-mediated inflammatory disease such as Sjögren's syndrome

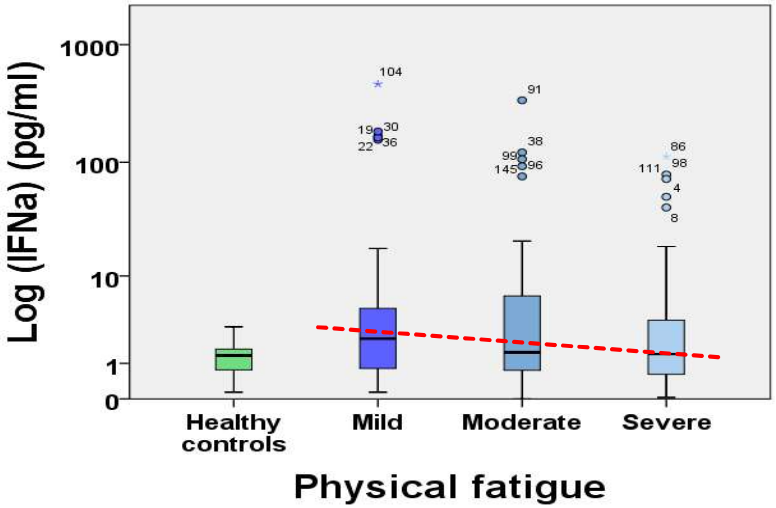
- Fatigue persists when patients in apparent clinical remission (i.e. no measurable systemic inflammation)
- Variability
- Many patients with clear evidence of systemic inflammation do not experience fatigue

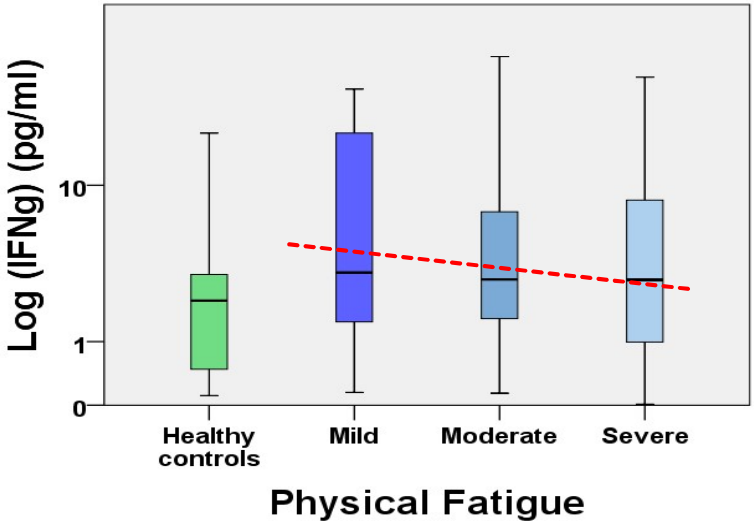
Newcastle University

Role of "conventional" inflammatory processes in fatigue in chronic disease remain to be defined







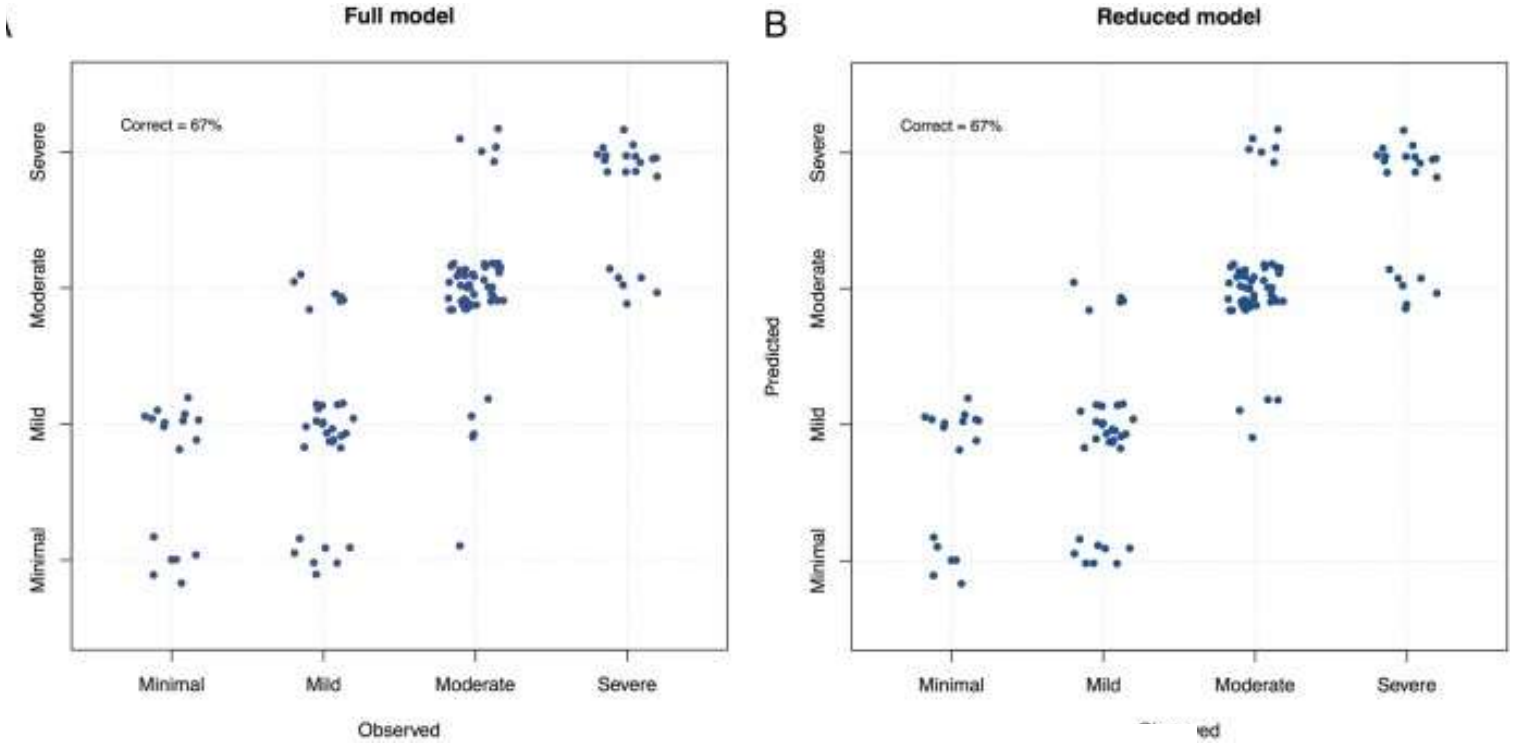


Howard-Tripp N, et al, 2016
Davies K, et al, 2019

SERUM PROINFLAMMATORY CYTOKINES IN PSS – REGRESSION MODEL

All parameters

Pain, Depression, IP-10, IFN-Y

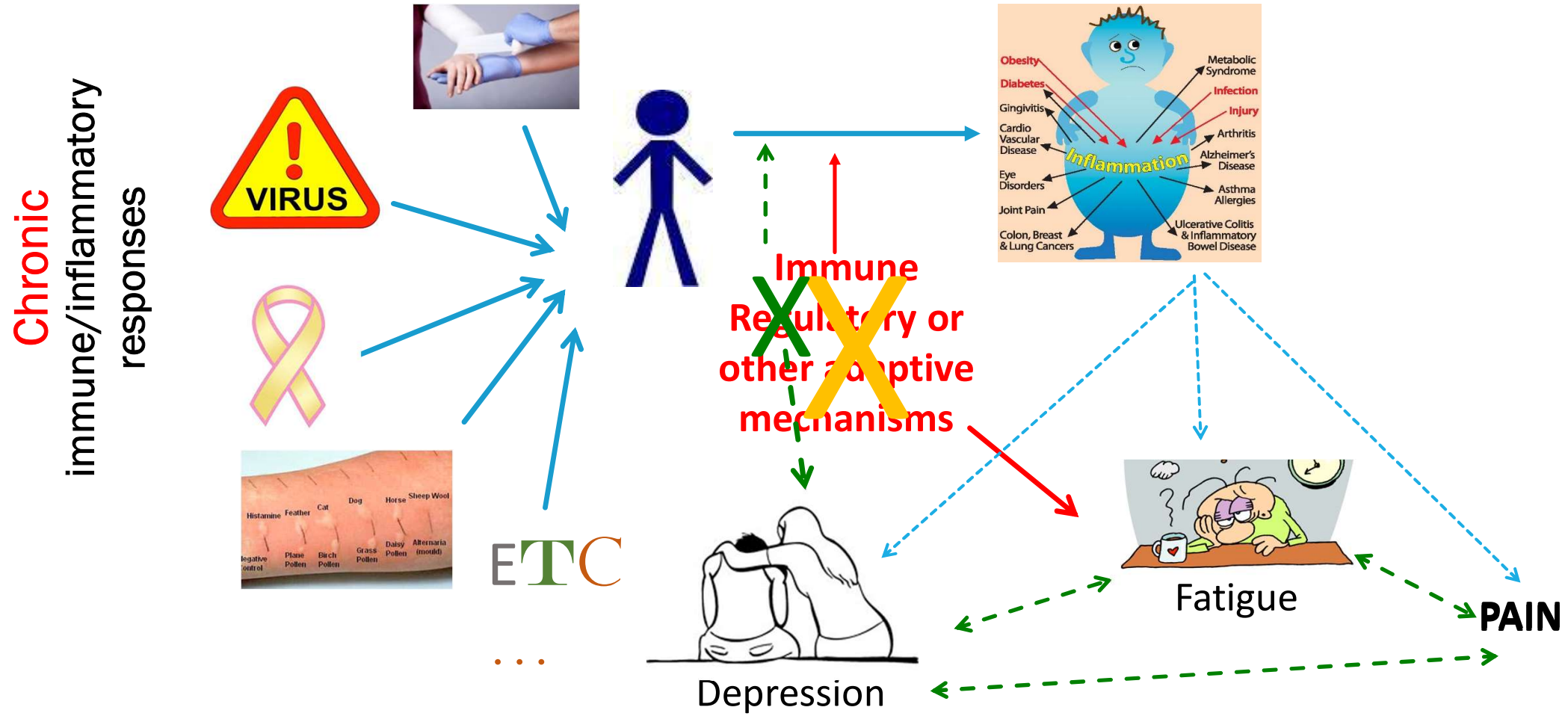


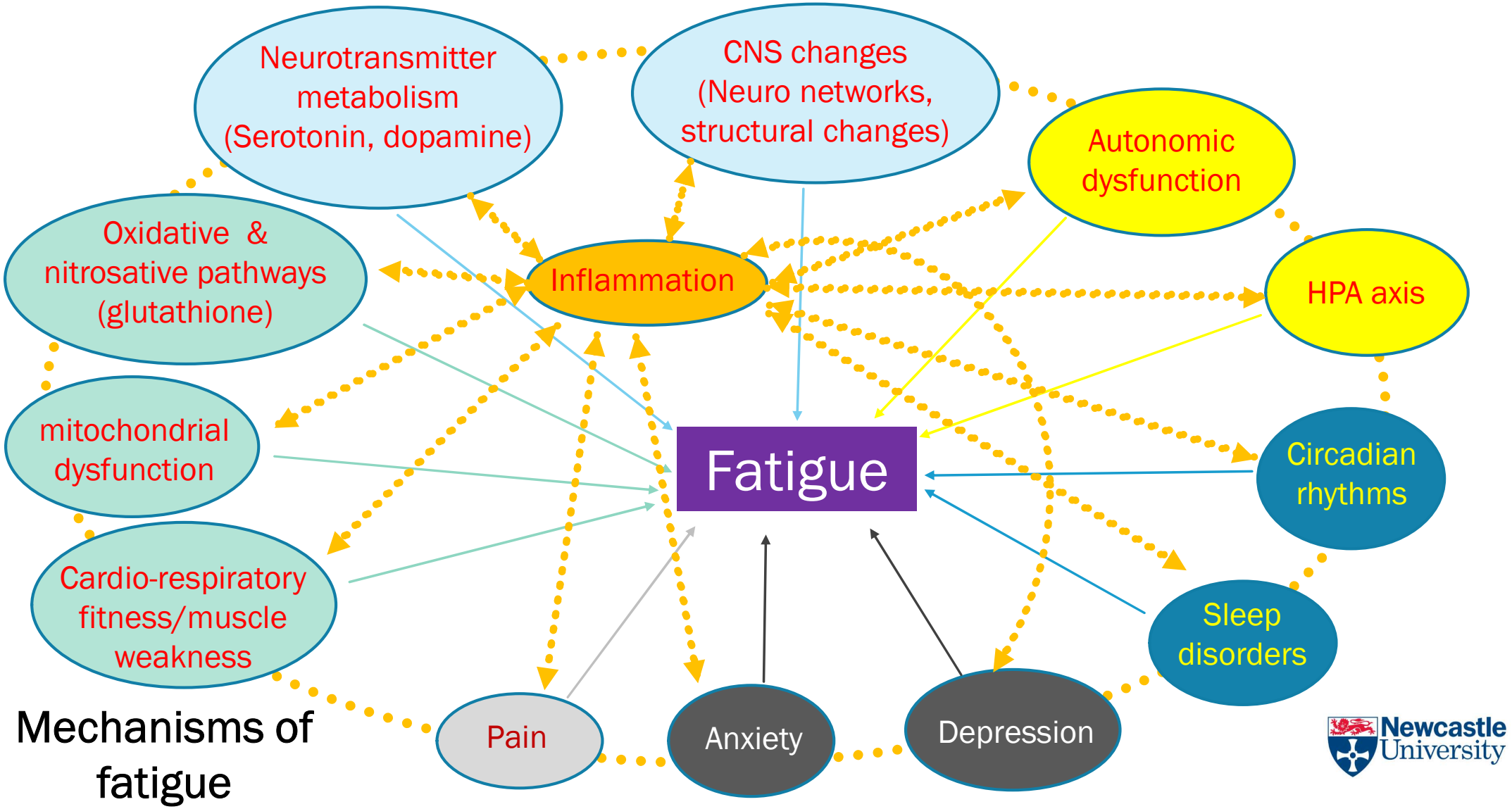
Predicted fatigue levels

Observed fatigue levels

Howard-Tripp et al, 2016

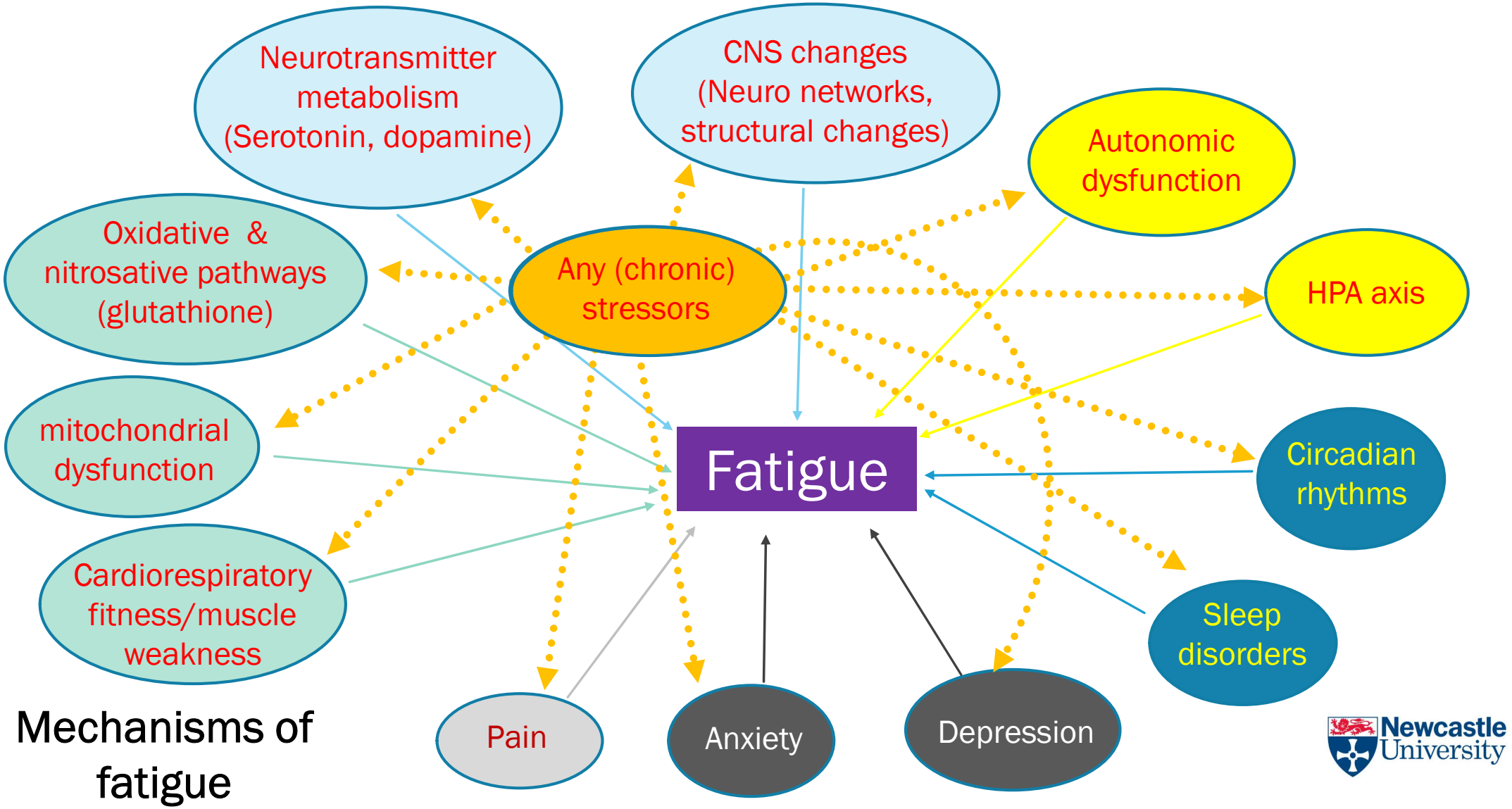
Physiological model of fatigue





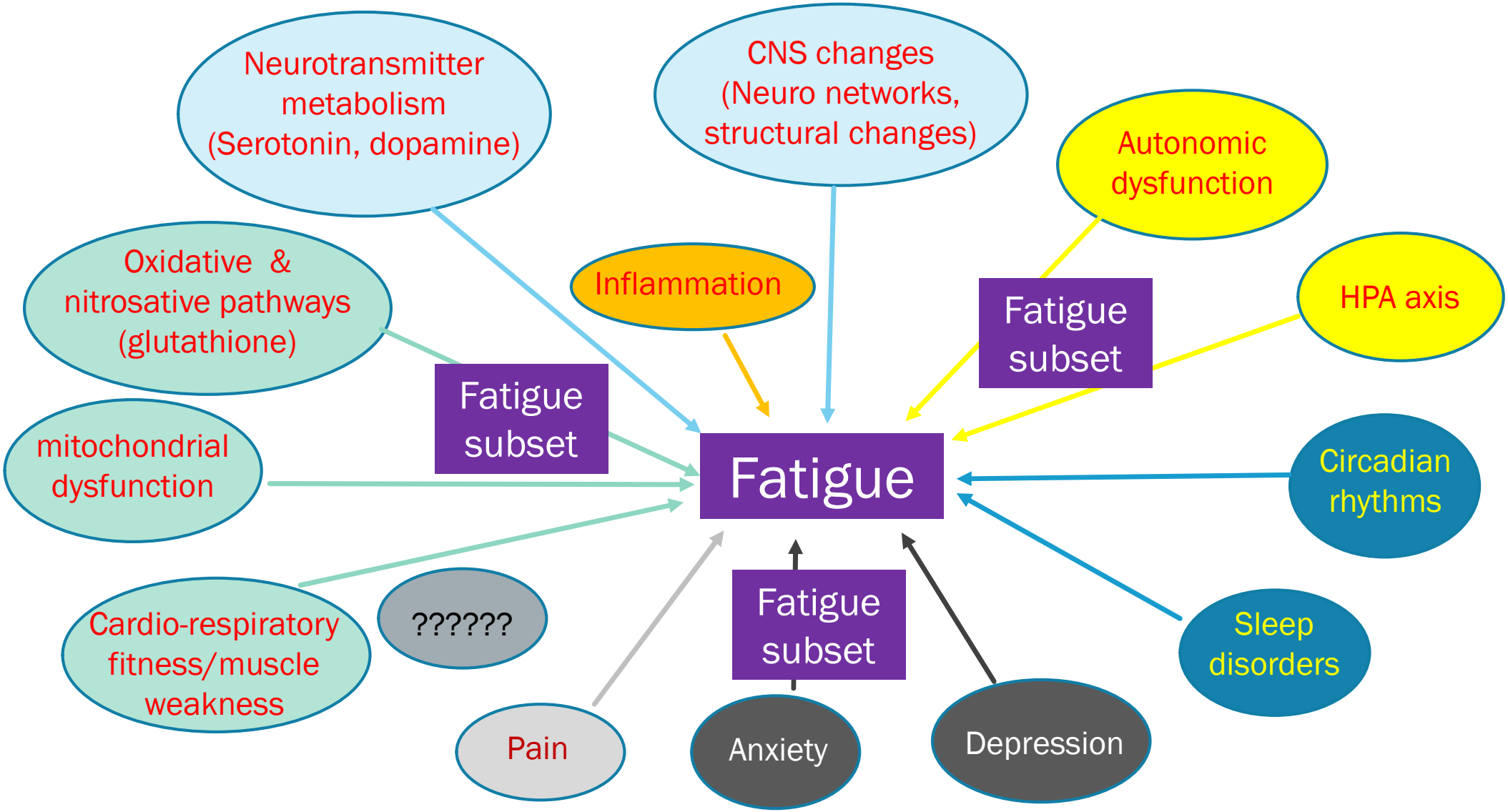
Mechanisms of fatigue

Newcastle University

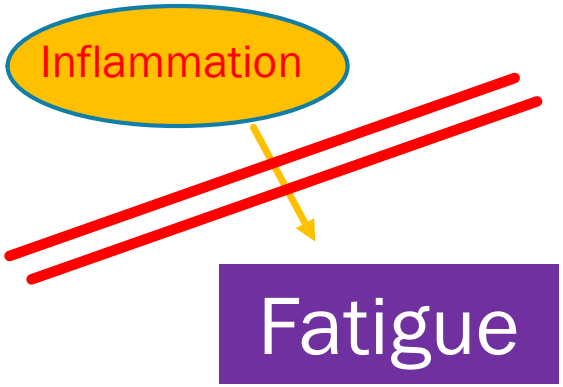


Mechanisms of fatigue

Newcastle University


Neurotransmitter metabolism (Serotonin, dopamine)
CNS changes (Neuro networks, structural changes)
Autonomic dysfunction
Oxidative & nitrosative pathways (glutathione)
Inflammation
Fatigue subset
HPA axis
Fatigue subset
mitochondrial dysfunction
Fatigue
Circadian rhythms
Cardio-respiratory fitness/muscle weakness
??????
Fatigue subset
Sleep disorders
Pain
Anxiety
Depression

TREATMENT OF FATIGUE



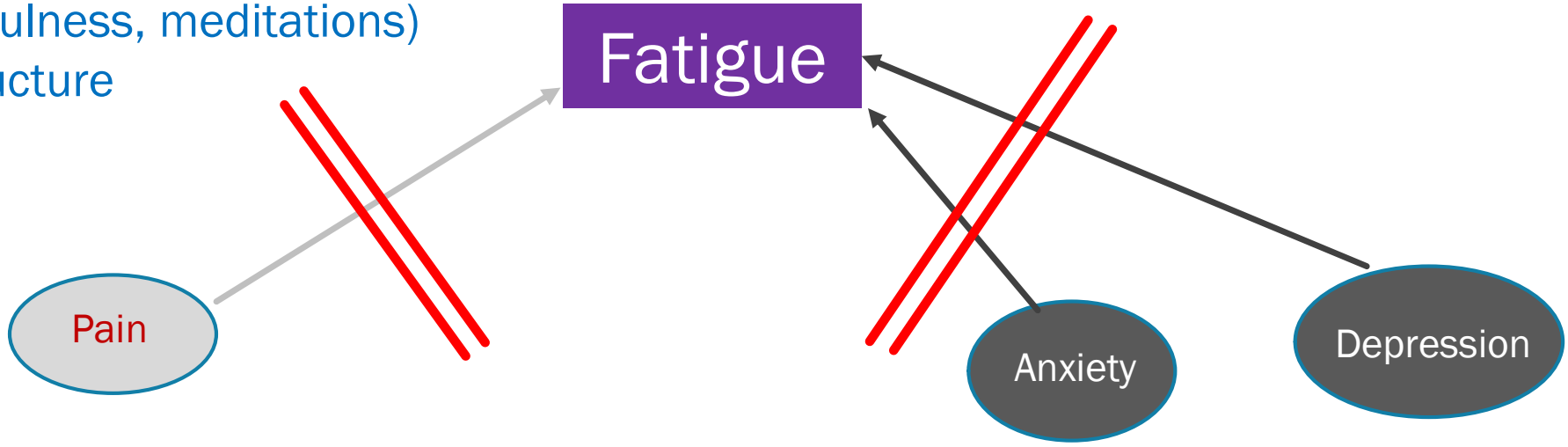
- Optimise immunomodulatory therapies to achieve clinical remission of the underlying inflammatory rheumatic disease
- Consider trial with hydroxychloroquine
- Avoid corticosteroid, especially long-term use or in non-inflammatory conditions

- *? Immunomodulatory therapies may be more useful in early disease or acute flares*

TREATMENT OF FATIGUE

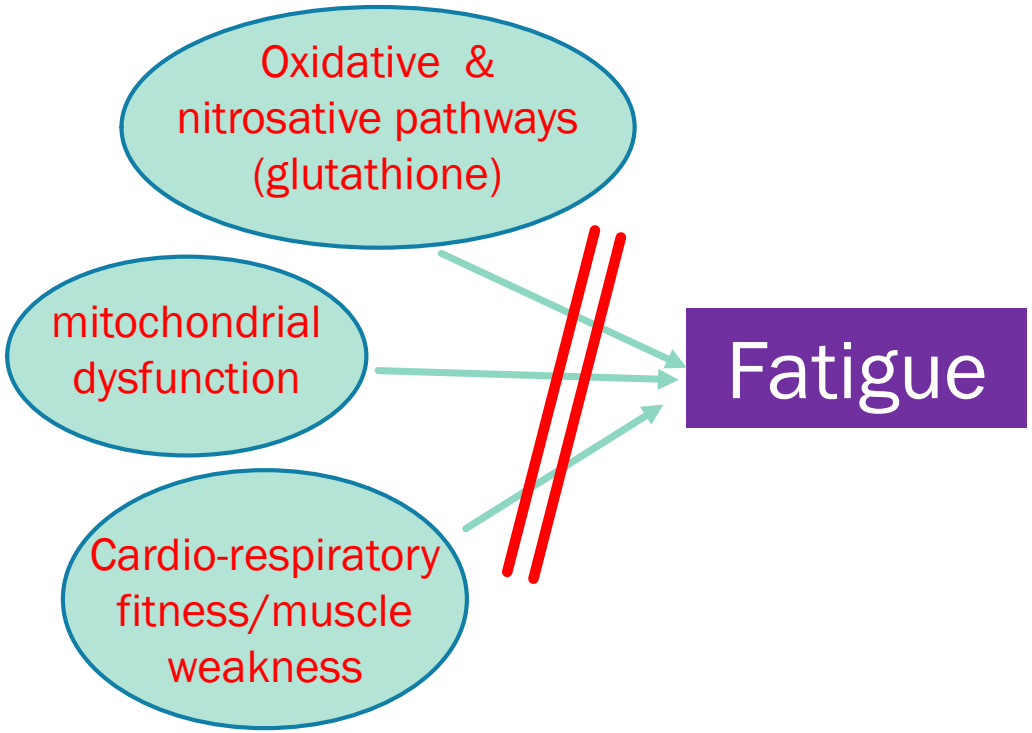
- Analgesics
- Pain modifying agents
- Pain management programmes
- Cognitive behavioural therapy
- Psychotherapies
- Other Mind-Body therapies (e.g. mindfulness, meditations)
- Acupucture

- Anti-depressants
- Cognitive behavioural therapy
- Psychotherapies
- Other Mind-Body therapies (e.g. mindfulness, meditations)
- Acupucture



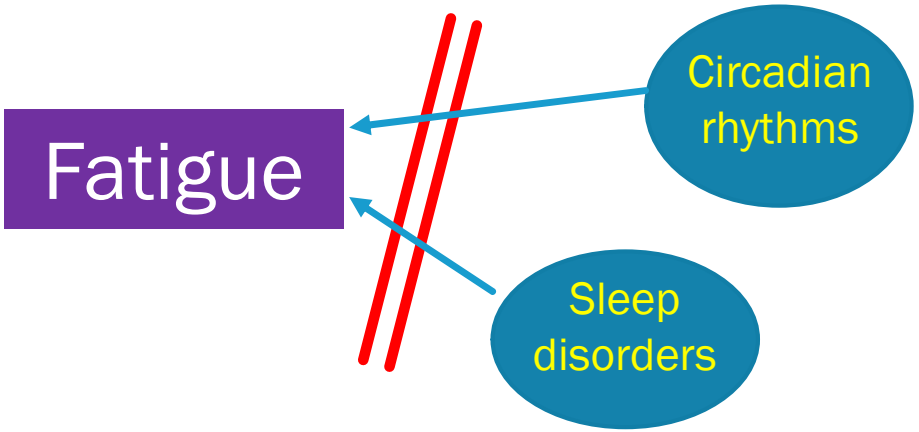
TREATMENT OF FATIGUE

- Exercises
  - Aerobic*
  - Resistance
- Supplements
  - Anti-oxidants (e.g. Vit E)*
  - Coenzyme Q10
  - Miscellaneous (e.g. turmeric, garlic, zinc, fish oils etc)



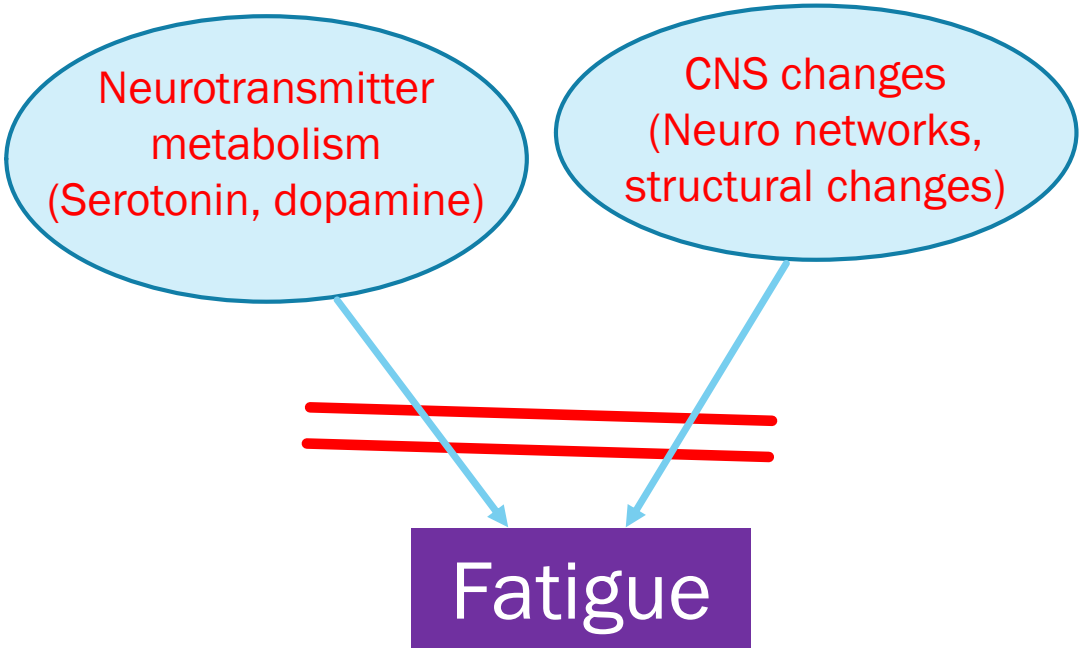
TREATMENT OF FATIGUE

- Treat any underlying sleep disorders
- Sleep education
- CBT-Insomnia
- ? Hypnotics
- ? anti-depressants
- ? Melatonin
- ? Modafinil
- Physical activities and exercise training



TREATMENT OF FATIGUE

- ? Psychostimulants (e.g. methylpehnidate, bupropion, amphetamine, epherdrine)
- ? Modafinil
- ? SSRIs
- ? Mind-body therapies



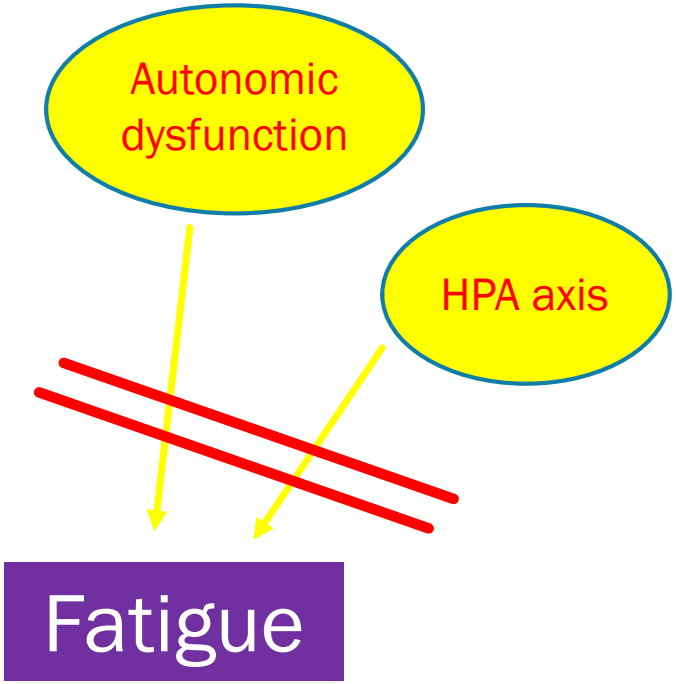
TREATMENT OF FATIGUE

HPA dysfunction

- ???
- ?? Low dose hydrocortisone/DHEA
- ?? Herbal medicine
- ?? Psychological medicine

Autonomic dysfunction

- ???
- Depending on symptoms, largely symptomatic
- For orthostatic symptoms (? Fludrocortisone, Midodrine, Droxidopa, Pyridostigmine)
- ? Vagus nerve stimulation



HOW TO MEASURE FATIGUE

CHALLENGES IN MEASURING FATIGUE

- Multi-dimensional
- “Severity” vs. “Impact”
- Variability
- “Momentary” vs. “average over a period of time”
- Confounders
- “Subjective” vs. “observed” or “objective” (“Perceived” vs “capacity” or “performance”)

Newcastle University

CHALLENGES IN MEASURING FATIGUE

Vary in different questionnaires

Unable to capture variability often experienced by patients

Multi-dimensionality
- No question assessing "mental fatigue"

Fatigue Severity Scale

During the past week, I have found that:	Agreement Score					
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6
2. Exercise brings on my fatigue.	1	2	3	4	5	6
3. I am easily fatigued.	1	2	3	4	5	6
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6

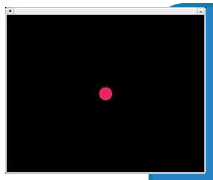
Perhaps more accurately or reliably assessed "objectively"?

Severity (Q8) vs Impact (Q9):
- But "impact" may depend on factors other than fatigue!

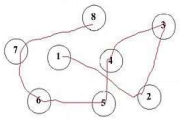
Confounders

In this questionnaire, the average score for someone with depression is 4.5, whereas the average score for SLE patients with fatigue is 6.5

POTENTIAL NOVEL APPROACHES TO MEASURING FATIGUE



Measure using psychomotor vigilance test?



Measure using e.g. trail making test, Stroop test?

Measure using accelerometer?

Measure aerobic capacity? Tracking heart rate and respiratory rate?

Modified Fatigue Impact Scale

		Never	Rarely	Sometime	Often	Almost Always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have trouble maintaining physical effort for long periods.	0	1	2	3	4

Newcastle University

NOVEL MEASURES FOR FATIGUE

- Several studies have shown impairment in neurocognitive performance in Sjögren's syndrome and other rheumatic diseases
- The results were not always consistent between studies
- Sample size tended to be small
- Most studies do not study the relationships between neuropsychological performance and fatigue
- Confounders may not be adequately controlled

NOVEL MEASURES FOR FATIGUE

- Kocer B et al showed impaired neuropsychological performance in Sjögren's
- Neuropsychological performance did not correlate to FSS or SF-36 vitality

But

- FSS has no practically no item on "cognitive" or "mental" fatigue, same for SF-36 Vitality domain!

SF-36 Vitality domain

23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

TABLE 2 Values of neuropsychological test performances in PSS and healthy control groups

	Patient (n = 32)	Control (n = 19)	p
MMSS	29.22±1.04	29.84±0.38	**.021**
Clock Drawing	6.44±0.80	6.89±0.32	**.029**
COWAT	25.59±10.19	33.74±9.72	**.007**
PASAT	46.97±8.49	51.84±3.64	**.007**
Stroop (second)			
Stroop1	33.91±9.23	30.09±3.09	**.038**
Stroop2	42.19±7.72	37.33±3.68	**.004**
Stroop3	32.80±6.79	31.86±4.50	.594
Stroop4	76.79±15.76	73.84±7.26	.368
SDLT	8.13±7.59	15.58±3.564	**.000**
AVLT			
Immediate (A1)	6.31±1.80	7.74±1.41	**.003**
Short term (A4)	11.41±2.00	11.84±1.17	.330
Short term (A5)	11.75±2.10	12.74±1.56	.081
Long term (A7)	10.34±2.28	11.42±1.31	**.037**
Recognition	41.63±4.49	41.95±2.35	.738
BNT	33.53±1.80	33.95±1.35	.387
BJLOT	21.03±3.82	24.63±2.19	**.000**
RCFT			
Immediate	17.88±7.45	23.37±4.21	**.001**
30 seconds	17.34±7.58	22.16±4.89	**.008**
30 minutes	17.28±7.23	22.68±4.30	**.002**
Recognition	19.42±2.42	21.26±1.49	**.004**

Kocer B, et al, 2016

NOVEL MEASURES FOR FATIGUE

- Impaired neuropsychological performance in Sjögren's syndrome
- No correlation between neurological performance and Fatigue Severity Scale

However,

- There were correlations between Sjögren's Mental fatigue score and Verbal memory (HVLT-R) and (close to statistical significant correlations) with attention, working memory and processing (DST, Trails B)
- HVLT-R is an independent predictor of the mental fatigue score.

Table 2 Cognitive performance in PSS patients and controls*

Test	All PSS Mean (SD)	Controls Mean (SD)	*P*-value	Effect size (Cohen's *d*)
Trails B	56.56 (5.56)	58.21 (9.73)	0.424	0.234
Stroop	53.50 (9.84)	58.13 (9.16)	0.114	0.472
WCST	47.91 (9.24)	50.07 (6.99)	0.422	0.248
Similarities	57.13 (8.446)	64.12 (8.703)	0.007	0.772
Boston naming test	54.08 (12.93)	56.94 (8.17)	0.406	0.245
DST	52.85 (8.52)	58.04 (6.02)	0.027	0.636
Controlled oral word association	44.21 (8.69)	47.95 (8.38)	0.143	0.398
Trials A	58.02 (5.62)	59.63 (7.22)	0.371	0.263
Verbal memory				
HVLT-R total	49.47 (7.62)	52.06 (8.27)	0.267	0.301
HVLT-R delay	49.19 (8.83)	53.24 (8.45)	0.121	0.458
HVLT-R % retained	48.81 (9.13)	52.76 (7.82)	0.130	0.446

Table 5 Linear regression model for cognitive SYMPTOMS (Prof-M) adjusted for age and depression in PSS patients

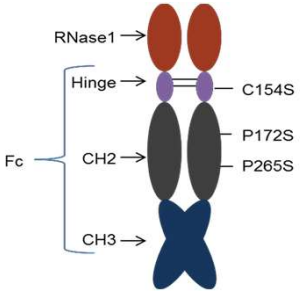
	R^2	R^2 change	*P*-value
Adjustors: age and depression (CES-D)	0.108	–	0.053
Verbal memory (HVLT-R) + adjustors	0.614	0.506	0.000002

Segal B, et al, 2012

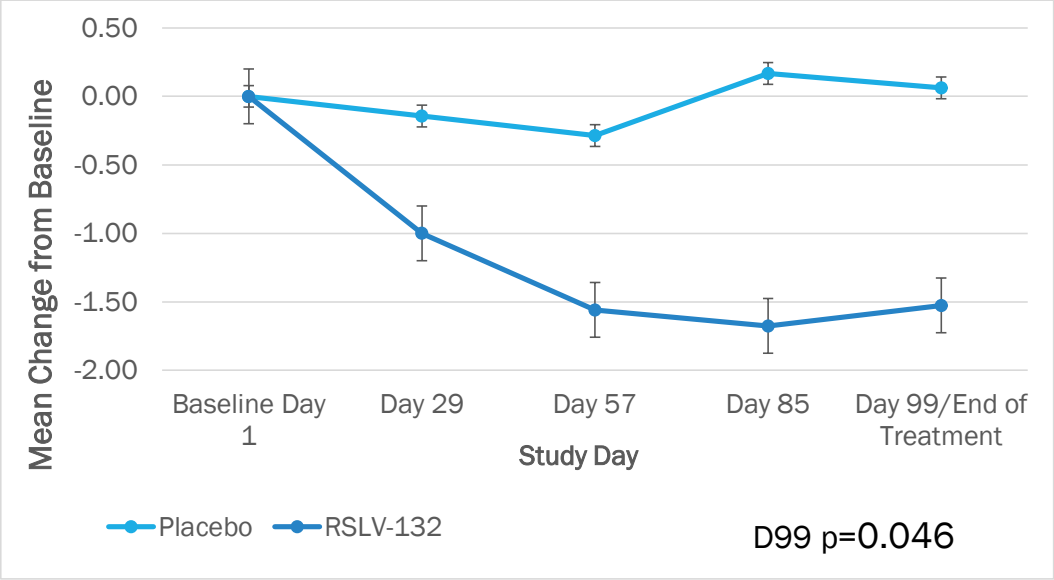
NOVEL MEASURES FOR FATIGUE

RSLV-132 is a First-in-Class Biologic (RNase fusion protein) to Eliminate Circulating Nucleic Acids

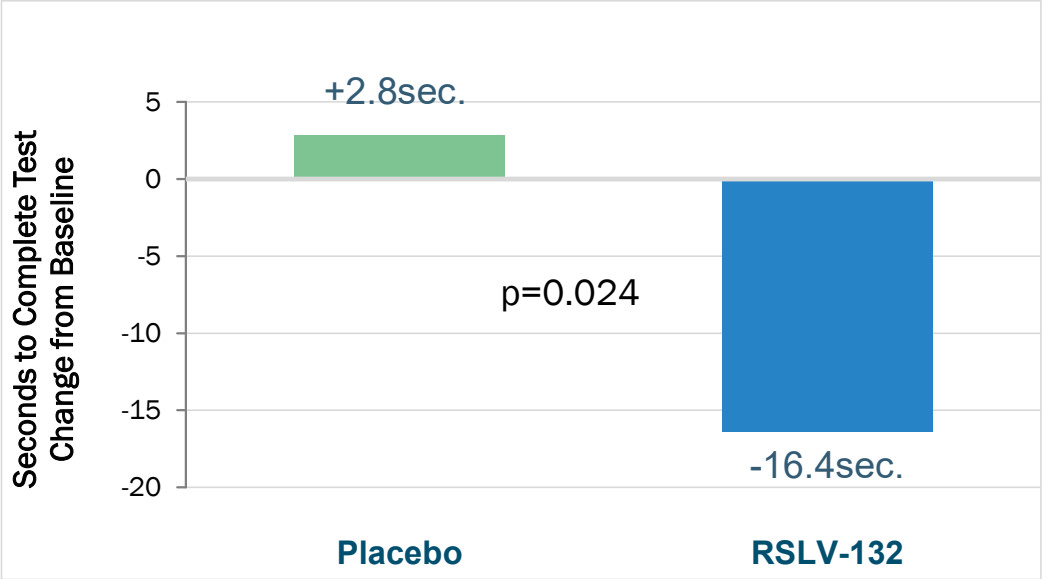
Posada J, et al, 2020



ProF: Improvement in *mental fatigue score*



Improvement in the performance of *Digital Symbol Substitution Test*



NOVEL MEASURES FOR FATIGUE

- Several studies have used accelerometers to measure physical activities in rheumatic diseases
- Several studies have also measure cardiorespiratory fitness and other assessment of physical capacity
- Relationship between fatigue was often not determined
- Confounders may not be adequately controlled

NOVEL MEASURES FOR FATIGUE

Dassouki T, et al, 2016

	pSS (n = 29)	*CTRL* (n = 20)	*CI* (95%)	p
Sedentary time (min/day)	493.8 ± 102.2	481.0 ± 103.5	−43.6 to 71.1	0.631
Sedentary time (% of wear time per day)	52.0 ± 10.9	56.4 ± 7.5	−9.3 to 1.5	0.161
Light PA (min/day)	375.1 ± 77.0	411.4 ± 106.2	−83.2 to 18.2	0.203
Light PA (% of wear time per day)	34.2 ± 7.7	31.6 ± 5.0	−1.2 to 6.2	0.186
Total MVPA (min/day)	26.3 ± 13.6	27.2 ± 12.2	−14.1 to 3.7	0.244
MVPA (min/day in ≥ 10-min bouts)	8.5 ± 8.5	6.0 ± 5.9	−88.9 to 35.9	0.409
Total MVPA (% of wear time per day)	13.7 ± 5.3	12.0 ± 4.3	−2.0 to 4.0	0.528
Total counts (counts/day)	653834 ± 161674	702106 ± 175975	−158198 to 31886	0.188
Mean accelerometer wear time (hours/day)	14.9 ± 1.1	15.3 ± 1.6	−1.3 to 0.4	0.338

- FACIT-F and SF-36
- TUG negatively correlate with SF-36 Vitality
- Only bivariate correlation was carried out
- Only crude measures of accelerometer data were analysed
- FACIT-F/SF-36 VT may not be the best questionnaire to explore these objective measurements and fatigue

	pSS (n = 29)	*CTRL* (n = 20)	*CI* (95%)	p
VO_{2peak} (ml/kg/min)	22.5 ± 3.5	24.6 ± 3.6	−4.2 to 0.0	0.05
HR_{peak} (bpm)	164 ± 14	172 ± 10	−15.6 to −0.5	0.037
Time to exhaustion (min)	12.3 ± 2.3	13.4 ± 2.1	−2.4 to −0.2	0.085
Leg press (kg)	105.2 ± 28.5	135.8 ± 54.6	−54.5 to −6.5	0.014
Bench press (kg)	19.9 ± 3.8	23.8 ± 6.1	−6.7 to −0.9	0.010
Hand grip (kg)	23.8 ± 4.5	26.6 ± 3.2	−5.1 to −0.4	0.021
Timed-Stands Test (reps)	14.8 ± 2.8	16.2 ± 2.6	−2.9 to −0.3	0.099
Timed Up & Go (s)	6.4 ± 0.8	6.0 ± 0.4	0.0 to 0.85	0.034

- Multi-dimensional
- Different questions

Similarly,

- Different objective measurements to capture different dimension/aspects of fatigue might be needed

FACIT-F

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

NOVEL MEASURES OF FATIGUE

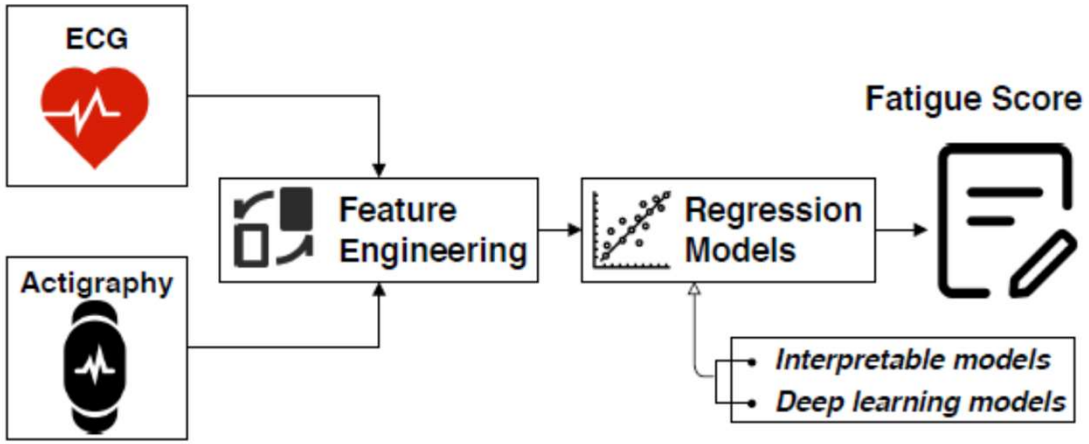


Figure 1: An overview of our fatigue assessment system

Yang B, et al, IWSC, 2020

Luo H, et al, Digital Biomarkers, 2020

IDEA FAST

IDENTIFYING DIGITAL ENDPOINTS TO ASSESS FATIGUE, SLEEP AND ACTIVITIES OF DAILY LIVING IN NEURODEGENERATIVE DISORDERS AND IMMUNE-MEDIATED INFLAMMATORY DISEASES

WWW.IDEA-FAST.EU

imi innovative medicines initiative

efpia

PARKINSON'S UK
CHANGE ATTITUDES.
FIND A CURE.
JOIN US.

Identifying Digital Endpoints to Assess FAtigue, Sleep, acTivities of daily living in neurodegenerative and immune-mediated diseases

15 European countries

18 Clinical / academic organisations

3 Patient organisations

Health Technology Assessment

IDEA FAST

6 Not-for profit organisations

10 EFPIA and associated partners

€ 42M

10 SMEs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

imi innovative medicines initiative

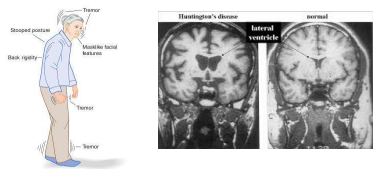
efpia

PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

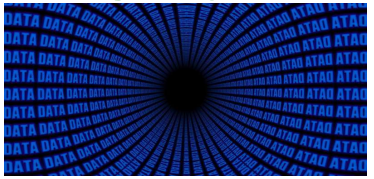
Disease of interests

Immune-mediated Inflammatory Disease

Neurodegenerative Disease



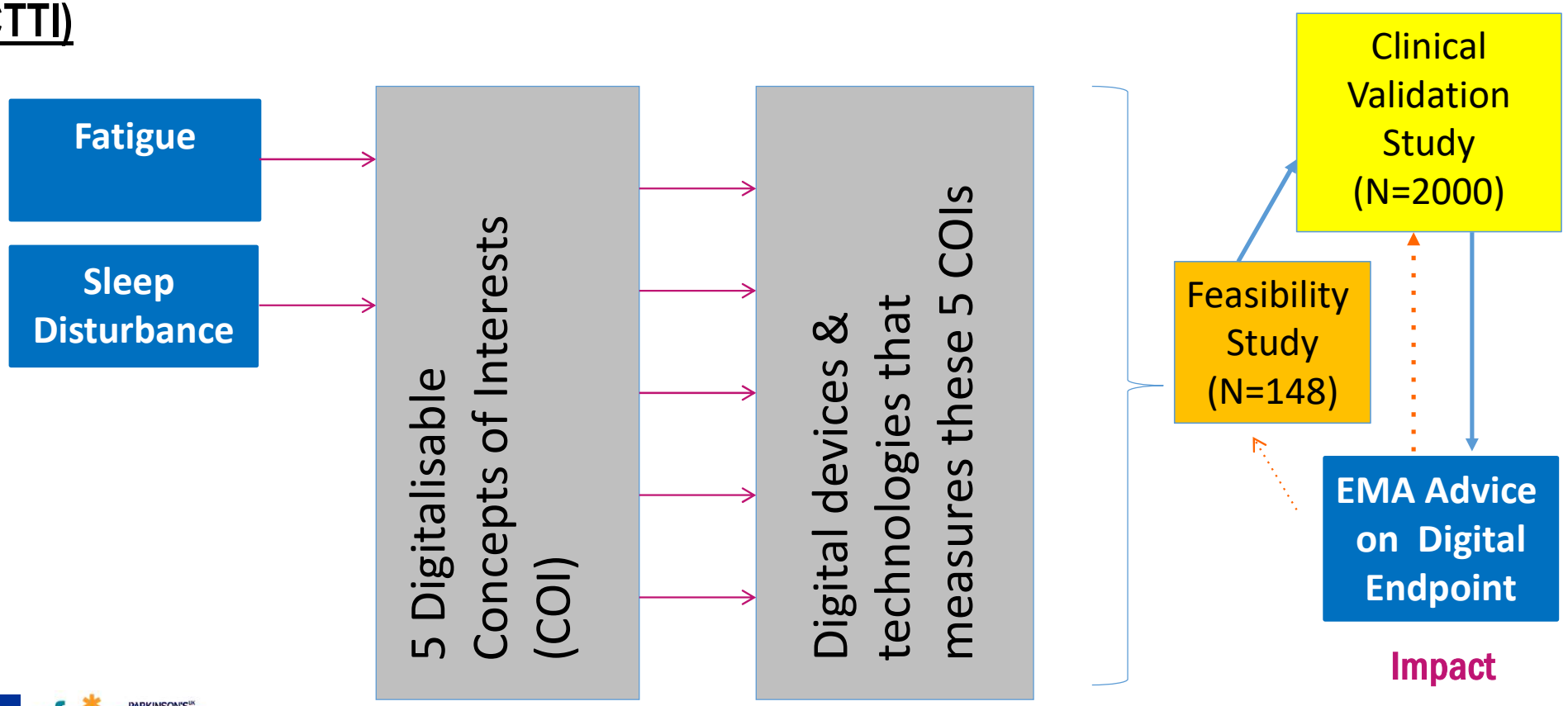
Lasting impact



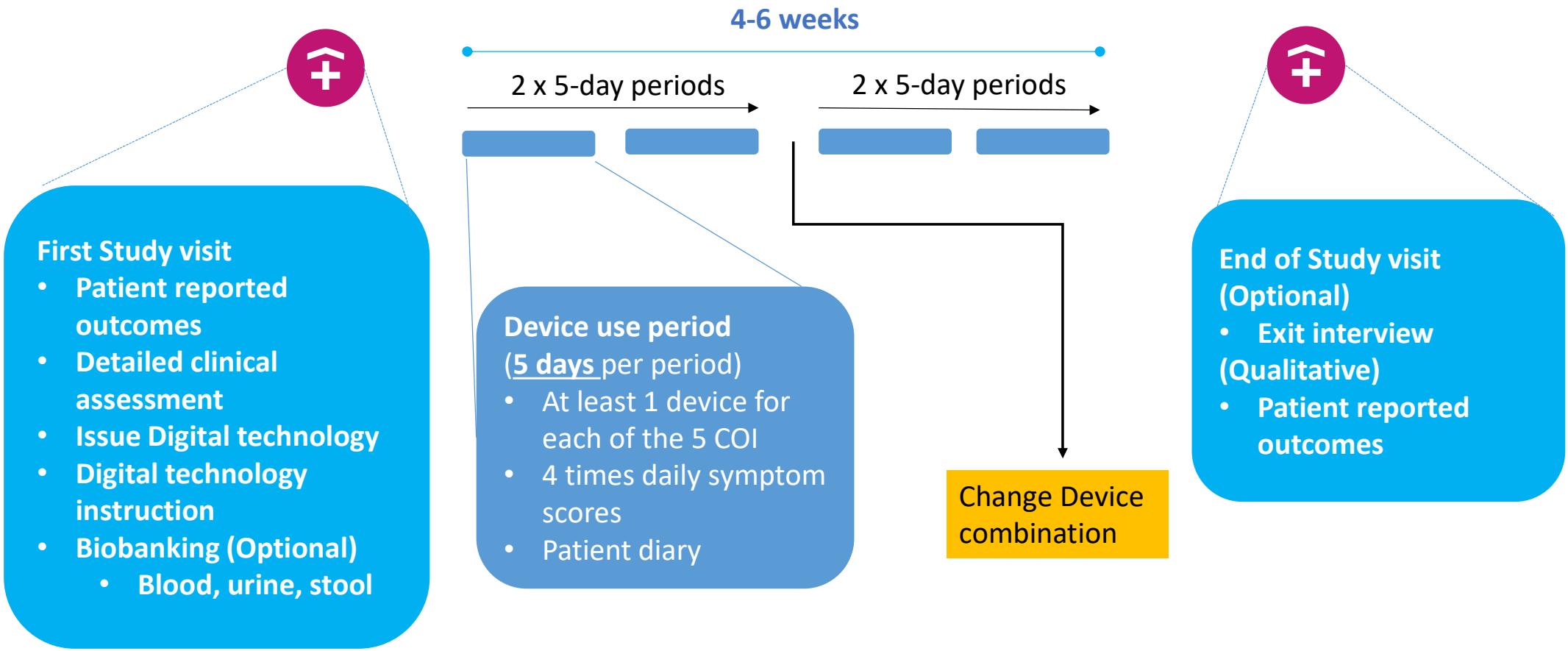
Real world clinical & digital datasets of 2200 subjects

Concept and Approach

Clinical Trials Transformation Initiative (CTTI)



Feasibility Study protocol

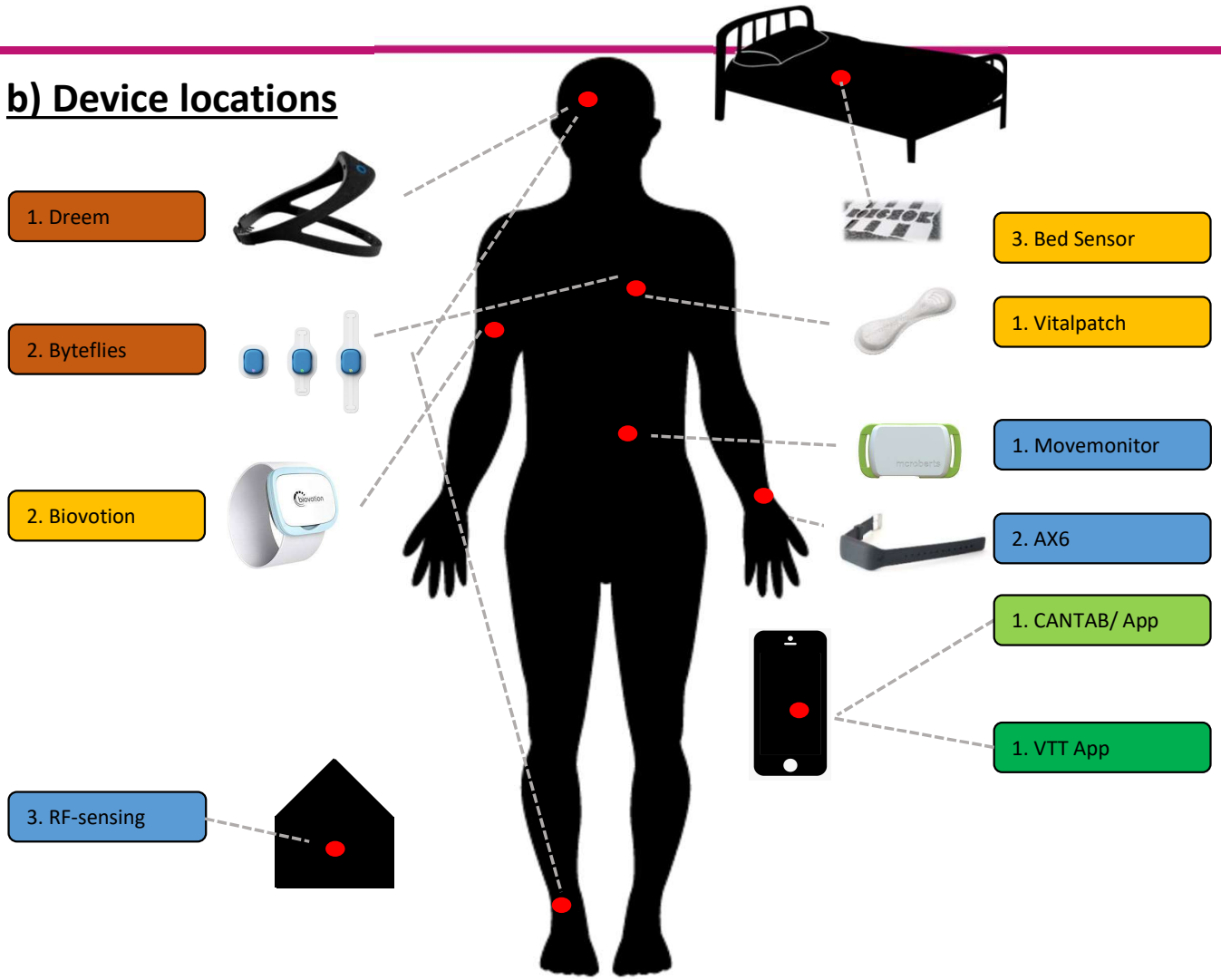


Feasibility Study Digital Technology

a) An example device combination across the timeline

	Cat\wk	1 (or 3)	2 (or 4)	3 (or 1)	4 (or 2)
"Permanent"	**A**	3	3	3	3
	B	3	3	3	3
	D	1	1	1	1
	E	1	1	1	1
Alternating sets	**A**	1 or 2	1 or 2	2 & 4 or 1 & 4	2 & 4 or 1 & 4
	B	1 (&2)	1 (&2)	4	4
	C	1	1	2	2

b) Device locations



CONCLUSIONS

- Fatigue is a syndrome that often coexist with other symptoms and there may be different “types” of fatigue or fatigue has different facets or dimensions
- Many questionnaires for fatigue exists, careful selection of appropriate questionnaire(s) to use in individual studies is important
- Considerations of confounding factors are critical in fatigue assessment and research
- Repeat/longitudinal measurement is useful (both in clinic and in research)
- Potentials for objective measurements of fatigue using non-invasive digital technology to complement questionnaire-based assessment.

CONCLUSIONS

- Management of fatigue remains a challenge
- Acknowledge the symptom and its impact is an important first step
- Multi-disciplinary, personalized and holistic approach is most likely required
- Begin with assessing potential contributing factors and devise targeted therapies accordingly
- Treat relevant comorbidities (e.g. anaemia, hypothyroidism)
- Effective treatments for most contributing factors remain elusive

ACKNOWLEDGEMENT

Kristen

Dennis

Jess

Emma

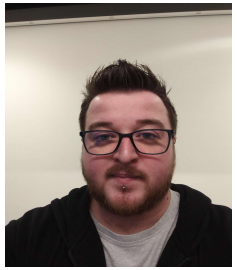
Vicki

Yang

Alexis

Nadia

Beth



Karl

David

ACKNOWLEDGEMENT

Acknowledgement

(Now VERSUS ARTHRITIS)

Sir Samuel Scott of Yews Trust

Patients & healthy volunteers

Thank you for listening

Newcastle University