Untangling the web of pain, fatigue and inflammation in autoimmune disease

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My Patients

- Systemic vasculitis
- Lupus
- Rheumatoid arthritis
- Axial Spondylarthritis
- Psoriatic arthritis
### Patient priorities: league table

<table>
<thead>
<tr>
<th>PRIORITIES LEAGUE</th>
<th>PRIORITIES LEAGUE</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PAIN</td>
<td>PAIN</td>
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<tr>
<td>2</td>
<td>2</td>
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<tr>
<td>Activities of daily living</td>
<td>FATIGUE</td>
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<tr>
<td>3</td>
<td>3</td>
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<tr>
<td>Mobility</td>
<td>Valued activities</td>
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<tr>
<td>4</td>
<td>4</td>
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<tr>
<td>Low mood</td>
<td>Low mood</td>
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<tr>
<td>5</td>
<td>5</td>
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<tr>
<td>Visible joint damage</td>
<td>Mobility</td>
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<tr>
<td>6</td>
<td>6</td>
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<tr>
<td>Valued activities</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>FATIGUE</td>
<td>Visible joint damage</td>
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</tbody>
</table>
Pain is the hallmark feature of Rheumatoid Arthritis (RA)
RA patients continue to report significant pain despite excellent control of peripheral inflammation

McWilliams et al (2016)
Could centralised mechanisms contribute to RA pain?

• FM prevalence
  • 13-25% of RA patients
  • 1-5% in the general population

• A further 7-15% of RA patients have FM features

Fibromyalgia is more than pain and is not a discrete construct
Fibromyalgianess (FMness) appears to be important in RA

• Challenging to phenotypically distinguish

• Unknown if FMness in RA is neurobiologically similar to ‘primary’ FM
Abnormalities in functional brain activity exist in fibromyalgia (FM)
Functional Connectivity (fc) MRI

- Examines statistical associations between the BOLD intensity time series of regions in the brain
- A number of network to regional functional connectivity abnormalities have been reported in FM
Default Mode Network (DMN)-Insula

DMN

- A constellation of brain regions thought to be engaged in self-referential thinking
  - Inferior Parietal Lobule (IPL)
  - Posterior cingulate (PC)
  - Areas of medial frontal Gyri (MFG)
  - Hippocampal formation
  - Lateral Temporal lobe

Insula

- Region of cerebral cortex ‘hidden’ within the lateral sulcus
- Integrates and converts physiological inputs into higher level outputs
- A key relay station in pain processing
DMN-Insula connectivity positively correlates with pain intensity in FM

Hypothesis

Rheumatoid arthritis patients reporting the highest levels of FMness will demonstrate similar fcMRI features to ‘primary’ FM, specifically DMN-Insula hyperconnectivity.
Aberdeen RA-Brain Cohort (n=54)

• Major inclusion criteria
  • RA according to ACR/EULAR criteria

• Multi-modal MRI brain
  • Structural
  • Functional (cognitive task)

• Clinical assessments
  • Inflammation (ESR, CRP)

• Questionnaires
  • Pain (Current VAS, FM)
  • Depression (Hospital Anxiety and Depression Scale)
  • Sleep (Jenkin’s Sleep Scale)
  • Fatigue (NRS)
Analysis

• Pre-processing
• Independent component analysis
• Network to whole brain analysis
  • ?connections which significantly correlated with Fmness spectrum
Clinical Characteristics n=54

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<table>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>54.9±11.41</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>13 (24%)</td>
</tr>
<tr>
<td><strong>DAS 28</strong></td>
<td>3.62 ±1.30</td>
</tr>
<tr>
<td><strong>RA duration (months)</strong></td>
<td>11.35 ±8.56</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>9.15 ±1.61</td>
</tr>
<tr>
<td><strong>CRP (mg/L)</strong></td>
<td>7.78±8.54</td>
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<tr>
<td><strong>Depression</strong></td>
<td>6.89 ±3.92</td>
</tr>
<tr>
<td><strong>Sleep disturbance</strong></td>
<td>15.67 ±5.46</td>
</tr>
<tr>
<td><strong>Current pain (NRS)</strong></td>
<td>3.81±2.38</td>
</tr>
<tr>
<td><strong>FMness</strong></td>
<td>13.20 ± 6.21</td>
</tr>
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</table>
DMN-Insula connectivity correlates with FMness among RA patients

Basu et al 2018
Clinicians require a point of care tool to quantify the contribution of centralised pain
Post-hoc analysis: Clinical associations with DMN-Insula fc

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>P value (age/sex corrected)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>0.002</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>0.13</td>
</tr>
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TRUMP
FATIGUE
See your doctor
Fatigue: a key patient burden

Fatigue is a principal determinant of

• Impaired quality of life
• Work disability
What do rheumatologists evaluate in the care of RA patients?

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Usually perform (%)</th>
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<tbody>
<tr>
<td>Joint examination</td>
<td>91.1</td>
</tr>
<tr>
<td>Grip strength</td>
<td>48.9</td>
</tr>
<tr>
<td>ESR/CRP</td>
<td>78.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10.3</td>
</tr>
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F Wolfe, 1999
Managing fatigue: Biologics

• British Society of Rheumatology Biologics RA Register (n=7000)

  • 70% with severe fatigue reported a clinically relevant (modest) improvement in fatigue (10 units SF36 VT) after 6/12 of biologic

  • Of those patients achieving full disease remission, 62.7% still reported significant levels of fatigue

*Druce et al* 2016, 2017
Non-pharmacological management: Lessening the Impact of Fatigue Trial
Where will we discover mechanistic origins of fatigue?
Peripheral Mechanisms: Skeletal Muscle MR Spectroscopy
Brain mapping fatigue

- Basal ganglia
  - Motivator of executive motor and emotional function
- Frontal lobe
  - Actioner of executive motor and emotional function
Fatigue is associated with hyperconnectivity between a number of brain networks and regions.
Fatigue is associated with increased basal ganglia grey matter volumes

- Neuroimaging method to quantify brain volume

- Fatigue significantly and positively correlated with PUTAMEN grey matter volume
Where next for neuroimaging and fatigue?

• Clinical stratification tool

• Delineate targets for future interventions
Example of stratification: Longitudinal RA Fatigue Course

![Graph showing mean fatigue (VAS 0-100) over time.](image)

- Baseline (n=341)
- 1 year (n=341)
- 2 year (n=328)
- 3 year (n=273)
- 4 year (n=138)

*Druce et al 2016*
Individual Trajectories of RA fatigue (Group Based Trajectory Modelling)

Druce et al, 2016
Employing baseline VBM metrics to machine classify fatigue improvers and non-improvers @ 6 months
Towards targeting:
Low grade current or magnetic brain stimulation??
Towards targeting: Exploiting clinical trials to optimise causal inferences: mediation analysis
Fatigue and inflammation
Brain mapping systemic inflammation

- Sickness Behaviour
  - Fatigue
  - Hyperalgesia
  - Emotionally vulnerable
  - Appetite loss
  - Sleepiness
  - Decreased motivation
  - Decreased locomotor activity
Cytokines/Inflammatory mediators

Blood Stream

CNS

BBB

Cytokines/Inflammatory mediators

Inflammation

Cytokines/Inflammatory mediators

Courtesy of A Schrepf
Multiple brain network-region connections are associated with ESR in RA

Schrepf et al, 2018
Medial prefrontal-cortex and inferior parietal lobule may be critical inflammatory ‘hubs’

Schrepf et al, 2018
Increased connectivity is associated with symptoms of RA

Schrepf et al, 2018
JAK-STAT inhibition provide superior pain alleviation compared to TNFα inhibition: RA-BEAM

Taylor et al, 2017
Where next?

• Validation
  • Cross-population (inflammatory disorders, general population)
  • Interventional (drug, brain stimulation)

• Granular immunophenotyping

• Granular neuroimaging

• Reverse translation
  • Genetics (UK biobank)
  • Animal models
Strategy for untangling the web

• Apply advancing neuroimaging technologies
• Exploit clinical trial frameworks to better understand human mechanisms
• Work in multi-disciplinary teams
• Embrace computing science analytics
• Reverse translate
• At every step, ensure that pathway to patient impact is clear
INFLAMMED EGO = PAIN AND FATIGUE