EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

Exploratory Workshop Scheme

Standing Committee for the European Medical Research Councils (EMRC)

ESF Exploratory Workshop on

Understanding the genetic, physiological and psychological mechanisms underlying disabling medically unexplained symptoms and somatisation

Munich (Germany), 10-12 September 2009

SCIENTIFIC REPORT

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1. Executive Summary

The workshop defined the most promising avenues of research concerning the aetiology and pathophysiology of "medically unexplained symptoms", somatisation and functional somatic syndromes (e.g. chronic fatigue and irritable bowel syndromes and chronic widespread pain). The workshop focussed first on commonalities and differences between symptoms and syndromes. We examined similarities and difference across functional somatic syndromes and somatisation in terms of genetics, stress physiology/ immunology, the effect of childhood adversities, central processing and response to treatment. The workshop then examined the possibilities of future collaborative research – what the aims of such a collaboration would be and how it could be realised.

The workshop brought together a multidisciplinary panel of researchers from several European countries to identify new avenues of research under 4 headings:

(a) Defining the phenotype for imaging, genetic and immune studies,
(b) Discussing ways of accumulating large population based studies and of identifying the new onset "cases" for intensive study,
(c) Examining possible new avenues of investigation using genetic, physiologically and, possibly, studies of childhood adversities.
(d) Discussing the possibilities/necessities for health service and other research that incorporates the socio-cultural differences concerning this field in Europe (including pathways to care and to chronic disorder).

This aim was achieved. 21 researchers from 7 EU countries contributed to a programme which was based on brief presentations of existing knowledge and ideas for further research. Each presentation was followed by a discussion, twice the length of the presentation, so that all participants contributed to all parts of the workshop.

The workshop results illustrate the currently still rather sporadic progress that is being made towards a fuller understanding of the aetiology of the functional somatic syndromes. It can be seen that research across several syndromes is more likely to provide useful information than research solely within one syndrome and that research into the classification and aetiology of numerous somatic symptoms could be usefully linked to studies of these syndromes. The field requires also, however, a constant re-evaluation of existing ideas and theoretical concepts as these are challenged by, for example, a re-examination of mediators in psychological treatment studies of chronic fatigue. The newer techniques, such as novel

measures of cardiac vagal tone or fMRI, need to be used in a creative way in carefully selected groups of patients where all important confounders are controlled if we are to learn which psychosocial variables are truly associated with which psychological or somatic ones. The rationale of the group formed in Munich is to develop such a co-ordinated series of studies. The chances of successful funding for such studies should improve now that the methods of research are becoming more sound and the importance of the functional somatic syndromes and somatisation as major causes of disability and high healthcare costs are being recognised.

2. Scientific Report

Functional somatic syndromes (e.g. chronic fatigue, irritable bowel syndrome and chronic widespread pain) have been studied primarily as individual syndromes to establish their aetiology. Over the last decade there has been a growing recognition that the syndromes have much in common including a female sex predominance, a close association with anxiety and depression and with stressful life events. Yet little research has considered the risk factors for several syndromes in the same study possibly because of the difficulty in getting research funding for several disorder simultaneously.

Recent findings from individual functional somatic syndromes that might be generalisable to other syndromes were illustrated by findings in functional gastrointestinal disorders and chronic fatigue.

Irritable bowel syndrome

Francis Creed (UK) highlighted the importance of “somatisation” (numerous bodily symptoms) as an important factor which is associated with marked disability and high healthcare costs. Lukas Van Oudenhove (Belgium) and Adam Farmer (UK) focussed on mechanisms underlying visceral pain hypersensitivity. It was demonstrated that the nature of variations in cardiac vagal tone in response to painful stimuli, appears to be associated with level of neuroticism. Using meta-analysis, Judith Rosmalen (Netherlands) was able to show that lower baseline cardiac vagal activity has been established in patients with various functional somatic syndromes with no apparent differences between chronic fatigue, irritable bowel syndrome and chronic widespread pain. By contrast a similar approach to HPA axis activity found evidence of lower cortisol levels in chronic fatigue syndrome and, possibly, in chronic widespread pain, but not in irritable bowel syndrome.

Chronic Fatigue

Research in chronic fatigue syndrome using cluster analytic techniques has established several subgroups, some of which have been also arisen from genetic studies. Peter White (UK) emphasised the need for repetition of this work in large, population-based studies which should be across functional syndromes not within a single syndrome. Review and re-analysis of data from randomised controlled trials of cognitive behaviour therapy (CBT) for chronic fatigue syndrome led Hans Knoop (Netherlands) to demonstrate that the positive effect of treatment is not mediated by increased physical activity, as previously thought. The beneficial effect of CBT on fatigue is related primarily to changes in illness related cognitions, including a discrepancy between perception and observed level of functioning, a difference which has been correlated with fMRI findings.

Diagnostic and classificatory issues

Existing diagnostic classificatory systems were found to be inadequate in this area of psychiatry so Per Klausen Fink (Denmark) and Bernd Löwe (Germany) examined new diagnoses that might be used in future work. The proposed DSM-V diagnosis of “complex somatic symptom disorder” may have the highest validity and clinical utility because it includes psychological and behavioural criteria and incorporates a dimensional approach to measure both somatic and psychological symptom severity. An alternative approach is based on somatic symptoms, which includes under the new diagnosis of “Body distress disorder” patients with all relevant syndromes. A measure of severity is the number of bothersome somatic symptoms, independent of diagnosis. This was found in a large, prospective population-based study reported by Ladwig and colleagues, to be predictive of poor outcomes, even after adjustment for a wide range of confounders including chronic physical diseases.

Genetic studies

Genetic studies are really in their infancy in this area because of an ill-defined phenotype but investigations to date suggest that there may be a genetic basis to some aspects of functional somatic syndromes. Specific symptom patterns and the presence of multiple somatic symptoms both appear to have more pronounced unique environmental effects than genetic ones (Pedersen and Kato). John McBeth (UK) reported preliminary evidence of associations between number of somatic symptoms and SNPs in the serotonin and HPA axis pathway genes.

Integration of findings

One way forward in this area of research is to seek specificity of association between psychosocial variables and psychological or biological responses. Preliminary findings suggest that childhood abuse is associated with a specific cerebral response to visual stimuli indicating pain, even after controlling for depression, anxiety and numerous somatic symptoms (Tölle and Gündel, Germany) but such closely controlled studies are rare. It was suggested (Rief, Germany) that this greater specificity would mean building on current knowledge, for example, of the genetics of pain sensitivity or immune response rather than examining the genetic associations of specific functional somatic syndromes, and seeking similarities and differences between somatisation and depression in view of the recognised difference in HPA axis reactivity (enhanced in depression but blunted or otherwise in functional somatic syndromes). In this way we should accept that some aetiological factors may be relevant to all functional somatic syndromes and some may be relevant only to one but, in addition, some may only apply in subgroups of patients within syndromes.

3. Assessment of the results, contribution to the future direction of the field, outcome

The group recognised that a number of design features for future studies include the following:

a) Two kinds of study design are required to measure predictors of change:

i. longitudinal population-based studies
ii. intervention studies

b) In both designs, it is important to measure a variety of functional symptoms and syndromes as outcomes, not just focus on a single syndrome or symptom as in so much previous research

c) Data analyses should, preferably, be directed towards trajectories of change (towards disease or remission), acknowledging important mediators (including psychopathology and medication use) and moderators (including DNA) and recognizing patient subgroups within the functional somatic syndromes

d) large samples are necessary to encompass all of these features and to perform satisfactory genetic studies.

e) functional imaging studies and studies of physiological parameters, e.g. response of the autonomic nervous system would benefit form using a common protocol at different centres and to included a wide variety of participants from different syndromes

To this end, several sub-groups were formed:

1. Uniform measures and diagnostic constructs sub-group makes suggestion for core set of instruments (Per Fink, Bernd Löwe, Winfried Rief)
2. Neuroimaging subgroup co-ordinates designs across different functional somatic symptoms (Lukas van Oudenhove, Adam Farmer, Harald Gündel, Thomas Tölle, Ralph Mager)
3. Population study sub-group collects information on existing and planned cohorts (Judith Rosmalen, Karl-Heinz Ladwig, Kenji Kato, Kari Ann Leiknes)
4. Genetics subgroup collects facts on existing datasets (John McBeth, Wendy Thompson, Nancy Pedersen).

As basis for further actions, the group discussed and agreed as a common aim of the group:

- to understand the common and specific aspects of diagnosis, aetiology and maintenance of Functional Somatic Syndromes (FSS)
- to develop und unify a field of research, using an integration of biological, psychological and sociocultural approaches
- this will enable us to improve prevention, detection and treatment of these syndromes

It was agreed that there would be a further meeting on 22nd/23rd March 2010 in Munich. There, further steps for submitting proposals within the ESF and/ or EU FP programmes will be considered.

Papers arising from presentations and discussions at the workshop will be published in a Special Issue (Eds. F Creed and P Henningsen) of the Journal of Psychosomatic Research approx. in May 2010.

4. FINAL PROGRAMME

Thursday 10 September 2009

Morning	*Arrival*
12.00 – 13.00	*Lunch*
13.00 – 13.15	**Welcome address** **Francis Creed** (Manchester Royal Infirmary, UK) and **Peter Henningsen** (Klinikumrechts der Isar, Munich, DE) and
13.15 – 13.45	**Presentation of the European Science Foundation (ESF)** **Janos Réthelyi** (ESF Standing Committee for the European Medical Research Councils - EMRC)
13.45 – 14.00	**Aims of the conference and the "one or many" debate** **Peter Henningsen** (Klinikumrechts der Isar, Munich, DE) and **Francis Creed** (Manchester Royal Infirmary, UK)
14.00 – 14.30	**Discussion**
	Session A: Aetiological research in single functional somatic syndromes
14.30 – 14.45	**Example 1: Studies in irritable bowel syndrome** **Francis Creed** (Manchester Royal Infirmary, UK)
14.45 – 15.15	**Discussion**
15.15 – 15.45	*Coffee / Tea Break*
15.45 – 16.00	**Rethinking studies concerning the neuroimaging and pathophysiology of functional GI disorders and pain perception** **Lukas Van Oudenhove** (University Hospital Gasthuisberg, Leuven, BE) **Adam Farmer** (Neurogastroenterology, St. Bartholomew`s Hospital, London)
16.00 – 16.30	**Discussion**
16.30 – 16.45	**Example 2: Findings in Chronic fatigue syndrome** **Peter White** (London School of Medicine and Dentistry, UK)
16.45 – 17.15	**Discussion**
19.30	*Dinner*

Friday 11 September 2009

09.00-09.15	**What have we learned from cohort and treatment studies in CFS?** **Hans Knoop** (Radboud University Nijmegen Medical Center, NL)
09.15-09.45	**Discussion**
09.45-10.00	**Genetic findings in population based studies of chronic widespread pain** **John McBeth** (Arc Epidemiology Unit, University of Manchester, UK)
10.00-10.30	**Discussion**
10.30-11.00	*Coffee / Tea Break*

Session B: Identifying common ground 1: diagnosis, classification and common factors

11.00-11.15	**Improving diagnosis and classification: body distress syndrome and alternatives"** **Per Klausen Fink** (The Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, DK)
11.15-11.45	**Discussion**
11.45-12.00	**Psychological processes common to the somatisation and related disorders"** **Bernd Löwe** (Universitätsklinikum Hamburg-Eppendorf, DE)
12.00-12.30	**Discussion**
12.30-13.45	*Lunch*

Session C: Identifying common ground 2: Possible new avenues of investigation using population based, genetic and physiological studies

13.45-14.00	**Population based studies of somatic symptoms** **Karl-Heinz Ladwig** (Helmholtz-Zentrum, Oberschleissheim, DE) and **Francis Creed** (Manchester Royal Infirmary, UK)
14.00-14.30	**Discussion**
14.30-14.45	**Perspectives of functional neuroimaging studies on pain in functional somatic and other syndromes** **Thomas Tölle** (Klinikumrechts der Isar, Munich, DE) and **Harald Gündel** (Medizinische Hochschule Hannover, DE)
14.45-15.15	**Discussion**
15.15-15.45	*Coffee / tea break*
15.45-16.00	**Genetic epidemiological studies of functional gastro-intestinal disorders and chronic fatigue** **Nancy Pedersen** (Karolinska Institutet, Stockholm, SE) and **Kenji Kato** (International University of Health and Welfare, Kanagawa, JP)
16.00-16.30	**Discussion**
16.30-16.45	**Stress physiology in relation to functional somatic syndromes in longitudinal studies** **J.G.M. Rosmalen** (University Medical Center Groningen, NL)
16.45-17.15	**Discussion**
17.15-17.30	**Genetic association and immunological studies in somatisation and somatic symptoms** **Winfried Rief** (Klinische Psychology and Psychotherapie, Universität Marburg, DE)
17.30-18.00	**Discussion**
19.30	*Dinner*

Saturday 12 September 2009

Session D: Future research

09.30-11.00	**General discussion of future research plans and how they will be implemented – chaired by Francis Creed** (Manchester Royal Infirmary, UK) and **Peter Henningsen** (Klinikumrechts der Isar, Munich, DE) i.e.: -Defining a list of research questions - Forming a central co-ordinating group - Practical steps
11.00-11.30	*Coffee / Tea Break*
11.30-13.00	**General discussion of future research plans and how they will be implemented – ctd.**
13.00	*Lunch*
afternoon	*departure*

5. Final List of Participants

Convenor:

1. **Francis CREED**
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6. Statistical Information on Participants

Countries of origin

United Kingdom	4
Denmark	1
Germany	6
Belgium	1
Netherlands	4
Norway	1
Japan	1
Sweden	1
Switzerland	1
Total	(20) – ESF representative not counted

Age Range (if known)

25-35	2
35-45	10
45-55	7
>55	1

Gender

Male	14
Female	6