

3. Description of the proposed research

3a. Research topic

Contemporary research of medically unexplained complaints (MUC) is mainly based upon studies with a limited view on causality, and is, instead of examining processes, mostly restricted to the study of physical and/or psychological states. Moreover, in general, those studies that are longitudinal are also retrospective, thus less reliable (Taylor, Jason and Curie, 2002). In addition, most research designs account insufficiently for the remarkable prevalence difference between women and men. Neither is there attention for differentiation in terms of age, social-economic status and ethnicity. Consequently, insight into the chronification process is incomplete, fragmentary and hardly specific for gender, age, class or ethnicity (Barsky and Borus, 1999; Sharpe and Bass, 1992; Kirmayer and Young, 1998; Nimnuan, Hotopf, Wessely 2001a; Wessely and Nimnuan, 1999). Therefore, it is impossible to develop theoretically sound interventions to prevent or disrupt chronification.

This research proposal aims to further the insight into chronification of MUC, and to improve the assessment of the risk of irreversibility as well as the theoretical underpinning for intervention studies.

MUC is a descriptive term for symptoms and syndromes for which health professionals can find no medical cause. Chronic fatigue, chronic pain, fibromyalgia and the irritable bowel syndrome are included in this category, for instance. Depending on the causal attributions implied these are also labeled as “functional somatic complaints”, somatoform disorders, conversion disorders etcetera. MUC have a high prevalence. The figures vary according to Nimnuan et al (2001 a) between one-third and two-thirds of the patients attending general medical clinics. The Netherlands are on the high end of this estimate. The authors cite Van Hemert and colleagues (1993) who found a percentage of 52% for a medical outpatient clinic. The comorbidity with mood disorders is high (Barsky and Borus, 1999, Wessely and Nimnuan, 1999).

Point of departure is the integrative etiological model of somatization verbalized by Kirmayer and Young (1998:423) as: “high levels of somatic distress in multiple functional systems can *arise* somatic amplification involving vicious circles of emotional arousal, bodily focused attention, symptom attribution, and cognitive appraisal. Those psychological processes are embedded in interpersonal and wider social processes that reinforce pathologizing symptom attribution and sick role behavior.” Thus, in the debate about whether commonalities among different MUC are more important, or the distinctiveness of each category of complaints (Deary, 1999), the current project joins the first category by searching for commonalities.

In particular, the project focuses on the influence of time and examines possible circular en non-linear causalities in chronification, as it is based on Non-Linear Dynamical (NLD) systems theory. Furthermore, the design will be prospective, bottom-up and gender- as well as age-conscious.

3b. Approach

Like general system theory, NLD starts from equilibrium, cybernetic principles of feedback and feedforward, self-regulation and deregulation. However, NLD equilibrium is considered to be dynamic. Only when fluctuations become too heavy or too frequent do instabilities occur. Then, the system may jump to a new equilibrium. Feedback mechanisms are assumed to contain not only circular but also non-linear causality: small differences in initial conditions may cause big differences in the end (or none at all) and the predictability of such outcomes is limited as well (Dijkum, 1997). Both insights apply similarly to the regulation loops. (Zouwen and Dijkum 2001).

Using NLD, one can explain transitions of quantitative into qualitative changes and develop indicators to predict those *order* transitions. NLD is therefore eminently suited to conceptualise the bio-psycho-social mechanisms underlying health and disease. In particular the transitions from acute into sub-chronic and from sub-chronic into chronic complaints can be modelled as a departure from the (health)

equilibrium, indicated by processes that show a strong increase or decrease in variability and complexity (Orsucci, 1995).

More concretely, the NLD-approach implies that chronic complaints are seen as the outcome of a deregulated equilibrium between two or more systems, including the physical system. Normally the biological, psychical and social systems are quite loosely coupled (Doornen, 1999). We assume that during chronification the intensity of the interaction between the systems will increase, eventually leading to resonance and synchronization of the systems' developments and resulting in critical fluctuations: some feedback and feed forward loops may speed up while others slow down, thus leading to a deregulation of the old equilibrium (Haken 1978; Schiepek, Weichrauch, Honerman, Jagdfeld, Kudwig-Becker, Petzold, Kroeger, 2001). Subsequently, one or more "new" loops may become dominant and lead to a different and 'less healthy' equilibrium (Dijkum, Mens-Verhulst, Kuijk and Lam, 2002; Mens-Verhulst, Dijkum, Kuijk and Lam, 2003).

The NLD - approach can be easily linked to the self-regulation framework for health and illness behavior of Leventhal, Nerenz en Steele (1984). This model assumes that the patients' processing of physical and mental symptoms will be active, parallel (in a cognitive and emotional pathway), in three stages (representation, coping and evaluation) and hierarchical (automatic and conscious, concrete and abstract, with a pressure toward consistency). The model has already been applied successfully in studying coping with complaints of fatigue (Heijmans 1998, Mens-Verhulst et al, 2003)

Moreover, the NLD model can be extended to other actors than "the self". It allows including the hypothesis that the chronification process is also stimulated and amplified by heteronomic steering of next of kin and of health professionals who base themselves – incorrectly – on the counter-effective model of (treating) acute complaints. (Bensing and Linders, 2003; Flor, 1990). As such the NLD approach is also very well compatible with the integrative model of Kirmayer and Young (1998).-

To study the dynamics of the biological, psychical and social systems we will use computer simulation because computers can compute and visualize non-linear relationships even though these cannot be solved analytically (Dijkum and Mens-Verhulst, 2002; Haefner, 1996).

As the computer simulation should serve to imitate a variety of risk-profiles, it should not represent an "average patient". Thus, stratification on basis of figures of prevalence for MUC will be applied. As MUC occur more often in women than in men and also vary with age (Bensing en Van Lindert, 2003; Blyth, March, Brnabic, Jorm, Williamson, Cousins, 2001; Mens-Verhulst and Bensing, 1997; 1998; Verhaak, Kerssen, Dekker, Sorbi, Bensing, 1998), gender and age will constitute the basis for stratification while the study will be homogenized for ethnicity. Such a gender-, age and ethnicity-conscious perspective will also be included in the literature study and in the compilation and analysis of the empirical data (Bekker 2003; Mens-Verhulst 2001a and b; Mens-Verhulst en Moerman, 2002; Leventhal, 1994). For reasons of cost and expediency the enquiry will be limited to an ethnically homogenous group of autochthonous Caucasian Dutch.

The model construction reckons with the possibility of a specific etiology per stratum, i.e. that there can exist a stratum-bound difference in the relevant feedback circuits and their composing factors and in the couplings and threshold values. For that reason, a bottom-up strategy will be applied, i.e. we will start with a specific type of complaints and a specific stratum, and gradually develop *the theory* into a "family of models". The project's PhD-trajectory will limit its focus to fatigue complaints of women in the age between 15 and 45 because these form the most prevalent group. Women who have a major psychiatric disorder (e.g. a depression or anxiety disorder) or a medical diagnosis that may explain their symptoms (e.g., heart problems, asthma) will be excluded from the study. When the first model has reached adequate validity, the intent is to follow it by the development of a male-specific version and by models for other complaints from the "fatigue-pain cluster" as empirically outlined by Nimnuan, Rabe-Hesketh, Wessely and Hotopf (2001b). However, that follow-up is beyond the scope of the PhD-project.

First, based on a literature study a *causal model* will be developed representing the relevant feedback circuits and their mutual coupling causal connections in a set of stages yet to be defined. Next, relevant variables will be designated and mathematical equations will be formulated to express the different types of causal connections in the distinct stages (see Dijkum and Mens-Verhulst, 2002;

Mens-Verhulst et al., 2003). Supported by system-dynamic software these variables and equations will be joined into a coherent *simulation model* that demonstrates how deregulations in (sub)systems may multiply into transitions and into a new dynamic equilibrium. The model *validation* starts with professionals and “patient experts” judging the face-validity of the computer simulation. It will be continued by comparing simulated data with real data, not only statistically but also regarding the curvilinearity, flexibility and variety of the time series (Dijkum and Kuijk, 1998; Kleijnen, 1999; Zouwen en Dijkum, 2001).

The empirical data for validation will be gathered prospectively from female patients (aged 15-44) who consult their general practitioner for the first time because of fatigue complaints. Recruitment will take place in the waiting room of five general practitioners, just like Rijk, Schreurs and Bensing (199.) successfully did. The precise number of patients will be defined later on. Measurements will take place during a year, with time-windows and sampling frequencies tuned on the course of the complaints and help-seeking. They will be done on a “real-time” basis using electronic diaries. (Bolger and Davis, 2003; Peters, Sorbi, Kruse, Kerssens, Verhaak and Bensing, 2000; Sorbi en Honkoop, 1996).

A patient who has agreed upon participation will be interviewed to explore her illness schemata regarding her fatigue as well as her social situation. Furthermore, she will be instructed how to keep the diary during 4 months, three days a week, once a day, resulting in 48 diary registrations. (Special actions will be scheduled to sustain her motivation.) The diary contains items on physical, cognitive and emotional experiences, coping and social events selected, for instance, from the Symptom CheckList and the Illness Perception Questionnaire. If permitted by the patient, information about her physical condition will be collected from her GP immediately after the first consult, with a possible follow-up after 6 months and 12 months. It is still to be defined if and how additional physiological processes can be registered of the patients who continue (presumably in the 6th week after the first consult) with further (specialized) medical consults and examinations. For this, our colleagues who are investigating the additional value of peripheral physiological measures for diagnosis and treatment of functional somatic symptoms will be consulted. (Houtveen en Doornen, 2002).

The collected data will be analyzed to reveal the within- and between- subject variation. Initially, we will use multi-level analysis. Also, whether and how the development of patterns in time can be described with linear multi-level models will be examined (Bolger & Davis 2003). In this way the necessity to work with non-linear models can be falsified (see also: Zouwen & Dijkum 2001); however, it is expected that further non linear pattern recognition is needed. ***Adequate NLD methods of analysis, such as recurrence plot, calculation of correlation dimensions, and the synchronization likelihood concerning the coupling of subsystems will be used to compute such models.*** (see for example: Schiepek, 2001; Stam, 2002; Webber, 1994). During the research it will be decided what software will be suited for those analyses.

Subsequent to the model validation, leveraging factors and starting points for interventions will be derived from the simulation. Finally, professionals and “patient experts” will be consulted to evaluate the applicability. Together, this will deliver a basis for intervention studies – on computer or ‘in vivo’ – that can result in advices to patients for self-management and to professionals for preventive or curative treatment.

<i>Planning? Zie apart document</i>
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Scientific setting.

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Main publications of applicants.....

Zie NWOLit2 of 3.

Setting within the Research Group.

The project will be embedded in the research-school Psychology and Health, more specifically area V, as filled in by the research team of de Health Psychology Department.

The mission of the Research Institute for Psychology and Health integrates the three following features:

- 1) Health research is approached from a broad psychological perspective incorporating social, developmental, cognitive and clinical psychology
- 2) The majority of the researchers combine fundamental and applied research approaches, and
- 3) Research focuses on mental as well as physical health.

Within this frame, Area Five is focused on psychological and psycho-physiological factors in adaptation to chronic illness. The Area conceives chronic illness as a stressor and studies the impact of coping with this stressor in the course of the illness. It concerns both the fundamental, strategic as well as the applied issues. The scope of study not only encompasses the impairing and health-enhancing behavioral patterns of patients but also the behavioral patterns of professionals in the medical settings. This area is also involved in translating psychological knowledge into interventions.

The Department of Health Psychology comprises a psycho-socially and a psycho-physiologically oriented researchgroup that both specialize in the study of chronic diseases, including the fatigue-pain cluster of the medically unexplained complaints.

Within the psychosocial research team – to which the first applicant belongs - the stress-coping framework is extended with notions from theories of self-regulation, and this is applied to the field of coping with chronic fatigue complaints. Building upon recently acquired insights it seems very appropriate to investigate the non-linear dynamics of regulation processes and the role of both patients and practitioners.

The team has considerable expertise on genderspecificity in complaints, copingstrategies, social-cultural contexts in patient-practitioner communication and in gender methodology. Furthermore, it has the necessary experience in interventionresearch with chronically ill patients. Taken together, this warrants a continuation of the model building also after the PhD-project is finished.

The psycho-physiological team has much experience with diary research. At the moment, it hosts the Veni-project “stress physiology and job-related functional somatic symptoms” in which non-intrusive physiological measurements are investigated to see whether they can provide additional information about the state of activity of the ‘central fear network’. Consequently, there is a good infrastructure available for this part of the project.

The already existing cooperation with NIVEL (The Netherlands’ Institute for Primary Health Care) at the level of the teams, department and the institute, will facilitate the necessary access to the general practitioners and their patients.

Output.

The project is aiming for a thesis consisting of minimally 2 articles submitted to international and peer reviewed journals, with a separately appended theoretical and methodological introduction and evaluation.

As from the second year we aim presentation of one paper a year on an international scientific congress with perhaps additional ones at the national level.

Presentations to other non-scientific forums will only be given insofar the research activities will demand it.

Societal & Scientific Relevance

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Relevance for patients and health professionals.1

The insights gained from the simulations will open up venues to understand and successfully manage the course of medically unexplainable complaints. This applies at first to women patients with fatigue complaints (the most prevalent group) but may also extend to other types of patients with MUC. As such, it will prevent unnecessary suffering and sustain the (health related) quality of life.

For professionals, the result will be an etiological model specially tuned for chronic complaints that will support them in a timely identification of patients that risk chronification. They can use the model to decide upon their interventions and references to other practitioners thus preventing further chronification. In addition, a gender and age conscious approach will enhance a client-oriented approach in health care.

On a longer term patients' increasing self-management and health professionals' timely and adequate interventions in chronification may lead to an important reduction of societal cost by both reducing the consumption of medical care and the number of missed labor hours.

Fit with national Council on Health Research

The project fits within the view taken by the Dutch Advisory Council on Health Research on pain research, namely that it should prioritize a) research into scope for the prevention of chronic pain, particularly through attention on the "careers" of patients with chronic pain, and b) improvement in pain-management i.e. coping with pain, through self-management and support from the patients' immediate circle of relatives and acquaintances, taking into account the effect of cultural differences, age and gender on the perception and management of (chronic) pain.

One may expect that the project will fit as well within the -still to be issued- report on chronic fatigue of the same council [Jozien vragen ? Of weglaten]

The scientific relevance.

The scientific relevance of the project is both theoretical and methodological.

It will contribute to theory about the "production" of chronification in cases of medically unexplainable fatigue, because of the enrichment of Leventhal's theory on self-regulation with notions from non-linear dynamics and because of the connection to a gender- and ageconscious perspective. In addition, the use of computer-simulation for the imitation of psychosocial processes can be regarded as an innovation in researching people with health complaints. In other areas of research (economy, sociology, biology and epidemiology) it is well known that the method of simulation allows escaping from dilemmas between a retro-and prospective and a mono- and multi disciplinary approach. Executing this research project can also shed light on the eventual constraints of the computer simulation method.

Finally, the proposed stratified approach in data collection, analysis, and simulation construction can have an exemplary effect on other health studies aiming at justifying bio- psycho- socio- cultural-differences.