Psychopathological analysis of several functional disorders and neurovegetative dysfunctions

Analiza psychopatologiczna wybranych zaburzeń czynnościowych i dysfunkcji neurowegetatywnych

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Abstract

The aim of the article is to present several conceptions on the functional disorders and neurovegetative (autonomic) dysfunctions. It was indicated that it is important to distinguish between these two concepts and to preserve this division in the newer classifications. The following syndromes were given as examples: neurocirculatory asthenia, Raynaud disease and bodily distress syndrome.

The current reflections were based mostly on foreign literature. The cited works largely focused on the issue of clinical psychosomatics, which may be a potential area of interest in neuropsychiatry.

The research carried out so far indicates that the concept of organ neuroses should be removed from the medical literature and rightly replaced with the concept of neurovegetative (autonomic) dysfunctions. Likewise, psychosomatic disorders begin to be understood as functional disorders. However, it becomes questionable to view these diseases as only one diagnostic unit, which is the bodily distress syndrome. They may have different health consequences and complications.

The nature of functional disorders and neurovegetative dysfunctions is still not well known. Several theories have arisen to explain them, but in general assessment they do not seem sufficient to use them *en masse* in clinical practice. Especially the development of neurovegetative dysfunctions should be constantly monitored, because, through the neurasthenic period, they can transform into severe organic disease.

Key words: functional disorders, autonomic dysfunctions, bodily distress syndrome, neurocirculatory asthenia, Raynaud's disease.

Streszczenie

Celem artykułu jest przedstawienie wybranych koncepcji dotyczących zaburzeń czynnościowych i dysfunkcji neurowegetatywnych (autonomicznych). Wskazano, że istotne jest zachowanie obu tych pojęć w przyszłych klasyfikacjach diagnostycznych. Omówiono przykładowe schorzenia wchodzące w ten zakres: astenię krążeniowo-oddechową, chorobę Raynauda oraz zespół dystresu cielesnego.

Zawarte wnioski oparto głównie na informacjach z zagranicznej literatury naukowej. Cytowane prace w większości skupiały się na obszarze psychosomatyki klinicznej, która może być potencjalnym obszarem badawczym w neuropsychiatrii.

Przeprowadzone dotychczas badania oraz praktyka kliniczna wskazują, że koncepcja nerwic narządowych (organoz) słusznie została przeformułowana w pojęcie dysfunkcji neurowegetatywnych (autonomicznych). Podobnie choroby psychosomatyczne zaczynają być od pewnego czasu rozumiane jako zaburzenia czynnościowe (funkcjonalne). Wątpliwe jest natomiast traktowanie zaburzeń czynnościowych i dysfunkcji autonomicznych jako jednej jednostki diagnostycznej, nazwanej zespołem dystresu cielesnego. Zaburzenia te mogą mieć odmienne powikłania i warto rozważyć skutki zniesienia tego podziału.

Etiologia zaburzeń czynnościowych i dysfunkcji autonomicznych jest niewyjaśniona. Powstały teorie tłumaczące ich naturę, jednak nie są one jeszcze wystarczająco rozwinięte, aby mogły być podstawą masowo stosowanych narzędzi diagnostycznych i terapeutycznych w praktyce klinicznej. Szczególnie warto rozważyć zagadnienie dysfunkcji neurowegetatywnych i ich monitorowania, ponieważ przez tzw. okres neurasteniczny w ich przebiegu zaburzenie autonomiczne może się rozwinąć w poważną organiczną chorobę układu nerwowego.

Słowa kluczowe: zaburzenia czynnościowe, dysfunkcje autonomiczne, zespół dystresu cielesnego, astenia nerwowo-krążeniowa, choroba Raynauda.

Introduction

Functional disorders (FD; sometimes called psychosomatic) (Burton et al. 2020) are a common problem in medical practice. Their scope may include many organ systems that produce symptoms which are specific to them. The nature of these diseases is described as organically unexplained (medically unexplained symptoms – MUS); therefore the subsequent implemented medical examinations do not give satisfactory results. The systems that produce these symptoms are as follows: cardiovascular, musculoskeletal, gastrointestinal, and nervous (autonomic). The most common symptoms from them are pain, fatigue, abnormalities in heart rate, nausea, hot or cold sweats and vomiting. Fibromyalgia is a particularly common pain condition. It can be estimated that 30% of visits in primary or specialist health care may result from FD symptoms (Nimnuan et al. 2001; Haller et al. 2015; Czachowski 2021).

In general, it is difficult to directly indicate the clear diagnostic procedures for fast assessment of FD. In the ICD-10 classification, prepared by the World Health Organization, there have been defined some diagnostic units, which may fall within the scope of FD. They are called as somatoform disorders (F45). The main characteristics of this group are:

- somatic symptoms, that provoke persistent calling for medical examinations,
- these medical examinations have negative results and symptoms have no organic causes,
- comorbidities do not explain these symptoms and their intensity.

This category includes the following diagnostic subunits: somatization disorder (F45.0), undifferentiated psychosomatic disorder (F45.1), hypochondriac disorder (F45.2), vegetative somatoform disorder (F45.3), chronic psychogenic pain (F45.4), other somatoform disorders (F45.8), and undefined somatoform disorders (F45.9).

The most basic from the F45 category is somatization disorder (SD). A variety of recurring symptoms must occur for at least 2 years. Through patient examination it becomes apparent that this person may have an extensive history of contacts with various physicians, who could not explain these symptoms on the basis of medical or anatomical tests. Distress, which is often present during experiencing SD, can be recognized as a risk factor for development of several mental comorbidities such as depressive or anxiety syndromes (Burton *et al.* 2020). In SD these syndromes are secondary to the func-

tional symptoms. It is possible to determine it by detailed clinical interview and analysis of history of diseases.

Etiology of these syndromes is unknown. Apart from psychophysiological stress reaction, research has shown that patients with SD tend to exhibit several attention disorders, which may be caused by decreased inhibition of afferent stimuli in the midbrain and brainstem, which can lead to insufficient filtration of insignificant somatic stimuli. Moreover, dysfunction of the cortical somatosensory regions, hypersensitivity of the limbic system on somatic stimuli and other abnormalities in the central nervous system functioning also have an influence on SD etiology.

In general, several interesting conceptions on FD etiology have been formulated. Nevertheless, they still require more scientific data for confirmation. Psychological analyses were concentrated on the adaptation and representation of individual disorders in patients' imaginary system (McAndrew et al. 2018). Certain mental categories, which could have an influence on increase or decrease of functional symptoms, were identified. In this model, patients who realized that their symptoms are formed in the psychological sphere had increased results of its presence and had more troubles with dealing with their symptoms. Moreover, factors which were named as "illness representation", "self-coping with threats", and "treatment results" were correlated with each other. Better understanding of perception processes, interpretation of the disease, and use of control strategies for maladaptive emotions by patients can reduce functional symptoms. Another theory that focuses on the processing and evaluation of information by the nervous system has some similarities (Henningsen 2018; Henningsen et al. 2018). It indicates that in FD there is a dysregulation between specific peripheral signals and their central assessment. Analytical structure of these signals can be interpreted as dangerous and threatening and has a negative influence on perception of these stimuli. This process could lead to the formation of FD, such as pain, nausea or vomiting. This system is called the "minimal prediction error model" (Henningsen 2018; Henningsen et al. 2018; Friston 2009).

Biological theoretical systems also have been developed. For example, chronic fatigue have been associated with hepatitic C virus (HCV), especially in first period of infection. There is a correlation between interferon α (INF- α) treatment of patients infected by HCV and chronic fatigue syndrome (CFS) (Russell *et al.* 2019).

Other research has indicated the important role of hypothalamic-pituitary-adrenal axis (HPA) dysregulation in CFS (Nijs et al. 2012). In addition, this conception also includes the importance of central sensitization, infection factors, and the negative influence of stressors in the hyperalgesia process in FD. Furthermore, the vegetative system was described as especially important in the development of FD in the example of fibromyalgia (Rizzi et al. 2017) and as hyperactivity of the autonomic nervous system in persistent fibromyalgic pain.

Molecular conceptions have been described also and they include: disorders in immunological responses, mitochondrial abnormalities, cytokine activation and regulation dysfunction, post-exercise dysfunctions in muscle cells, and activation of enzymes from the group of kinases. Mitochondrial dysregulations can manifest as metabolic disorders in FD. It may be possible that these metabolic properties could serve as potential biomarkers (Tomas and Newton 2018). These mechanisms may be potentially linked with a central sensitization phenomenon, which was considered in FD pathophysiology (Bourke et al. 2015). It seems to be similar to chronic primary pain disorder, which is listed in the ICD-11 classification (Nicholas et al. 2019). It is possible that FD are a group of differential and polyetiological syndromes, which should be discussed in more individual dimensions.

Organ neuroses (organoses) – a discussed classification issue

The term "organic neuroses" may be misleading, because it potentially suggests that neurosis is concentrated on the individual organ. From a psychophysiological point of view, the main cause of organoses is located in the cortex. The search for their conditions should be concentrated on special and individual dispositions and periods, when symptoms are the most intense.

The phenomenon of the neurasthenic period should be considered in this area. This is a period of time before the development of severe syndromes of the central nervous system or general diseases. Organoses seem to be a type of predictive functional symptoms as the neurasthenic period. Neglect of preventive treatment may lead to the progression of the main syndrome. For instance, gastric ulcer and duodenal ulcer, which can develop by long-term gastric secretory disturbances, caused by central abnormalities, can be indicated. Usually, it begins with stomach neurosis. Therefore, this neurosis is not caused

by inefficient stomach function, but by disorders from the central nervous system. Moreover, it is not only the neurosis of an individual organ, but always general. Adler's psychoanalysis defined it as just psychogenic disorders, or "conversive" psychoneurosis.

As a medical knowledge developed, the role of the neurovegetative system was noticed. The term of "organoses" was conceived for neurovegetative dystonia or autonomic disorders (dysfunctions; ADS) in the somatic form (F45.3; ICD-10 from World Health Organization). In this case, treatment with psychoanalysis is not advisable as it may be a predictive period before an organic disease, as mentioned above.

Probably, the problem of organoses is associated with the conception of Pavlov's "weak nervous system", which can determine the susceptibility to neurotic symptoms as follows: vasomotor hypersensitivity, slow heart rate in deep squat or bending (Erben symptom), tendency to psychogenic blushes (erythema pudendi), pulse slowing down when pressure is applied to closed eves (Aschner symptom), orthostatic tachycardia, respiratory arrhythmia features of spasmophilia (Chvostek), tenderness of peripheral nerve trunks, compressive head sensations (Charcot's casque), prolonged dizziness, tendency to allergic reactions or tendency to faint (Bilikiewicz 1979). This could explain some of the functional symptoms in organosis course. Moreover, it could condition the susceptibility to other FD types.

In the ICD-10 classification, precise diagnostic criteria for ADS were indicated: persistent symptoms of autonomic excitation (increased heart rate, trembling, reddening); additional subjective symptoms related to the system or organ; excessive concentration on the possibility of serious damage to the organ and its unpleasant experience, despite the explanations of the medics; and no confirmed, significant disturbances in the structure or function of a given organ. They can be grouped into four classes by their appropriate localization:

- heart and circulatory system: neurocirculatory asthenia, heart neurosis, Raynaud syndrome, Da Costa syndrome,
- respiratory system: globus hystericus, psychogenic respiratory syndrome (hyperventilation, paroxysmal cough, hiccup),
- gastrointestinal system: aerophagia, stomach neurosis, cardiac orifice spasm, indigestion, irritable colon, psychogenic diarrhea,
- genitourinary system: psychogenic increase in frequency of urination, neurogenic bladder, dysuria, involuntary bedwetting.

This division seems to be very similar as indicated in the bodily distress syndrome definition. The ICD-11 defines it as a group of symptoms from several organ systems (multi-organ type) or one organ system (single-organ type). Thus, this divides the symptoms into the following classes (Fink *et al.* 2007; Budtz-Lilly *et al.* 2015):

- cardiopulmonary and autonomic arousal: palpitations, heart pounding, breathlessness without exertion, precordial discomfort, hot or cold sweats, trembling or shaking, dry mouth,
- gastrointestinal arousal: frequent loose bowel movements, feeling bloated, full of gas, heavy in stomach, abdominal pains, nausea, vomiting, burning sensation in chest or epigastrium,
- musculoskeletal tension: pains in arms or legs, feelings of paresis or localized weakness, back ache, pain moving from one region to another,
- general symptoms: fatigue, impairment of memory, dizziness, concentration difficulties.

Fink indicated that it is possible to use the term and definition of bodily distress syndrome to include almost all functional disorders (Fink and Schrörder 2010; Ivbijaro and Goldberg 2013). Indeed, recent research showed that numerous diagnoses of FD, specified in current diagnostic classifications, belong to a family of closely related disorders (Budtz-Lilly et al. 2015). However, by introducing this category, there is a fundamental problem as to whether it is not too general. The nature of FD is not understood as well, and individual treatment systems for each condition may vary and be based on different principles. Putting everything in one category may result in these diseases being regarded too radically as one. In particular, one should be careful with over-treatment of neurovegetative dystonia and somatization disorder, especially as the first one may herald a serious nervous system disease, while the second one will have more psychogenic nature.

An example of a widely distributed ADS is neurocirculatory asthenia (NA) or Da Costa's syndrome. This is a disorder of unknown origin, which is characterized by palpitations, pain, shortness of breath, rapid pulse, dizziness, headache, disturbed sleep and digestive disorders (Fava *et al.* 1994). Existing pain manifests as chest discomfort not typical of angina pectoris caused by ischemic heart disease and usually it occurs in paroxysm (Da Costa 1871). Other psychocardiac disorders were sometimes described as the part of NA, for example, the following diseases: hyperkinetic heart syndrome, atypical chest pain with normal coronary arteriograms, or hyperdynamic β-adrenergic circulatory state.

Chronic character of the NA can significantly influence activity of patients. If Pavlov's weak nervous system conception, described above, is adequate, the NA could be described as a maladaptive property of the patient's nervous system and can condition his further cardiac complications. Moreover, NA seems to be especially associated with anxiety and anxiety disorders. This state informs about potential psychogenic dimension, besides the neurovegetative part. It can be suspected that NA is the result of interaction between neuronal susceptibility and personality features, for example a high neuroticism level.

Another ADS phenomenon is Raynaud disease (RD), which concentrates on the paroxysmal bruising and paling of the fingers. It should be noted that RD and Raynaud syndrome are not the same term. RD is present when occurring symptoms have no organic cause and their etiology is functional, while Raynaud syndrome is caused by, for example: injuries, nervous diseases (syringomyelia, prolapse of the nucleus pulposus, peripheral neuritis), pressure on arteries and nerve trunks (cervical rib), arterial diseases (atheromatosis, Buerger disease), or poisoning (for instance, heavy metals).

The etiology of RD is unknown. Among the theoretical considerations, the inherited hypersensitivity of the arteries of fingers is indicated. Other discussions focus on changes in the vasomotor centers in the spinal cord, chronic irritation of the spinal nerves at the brachial plexus and cervical spine, or excessive adrenaline secretion. Symptoms usually occur in young, neurotic women. Already in childhood, their hands may be very sensitive to cold. The clinical course of the disease includes the fingers suddenly becoming pale, except the thumb, and it progresses to the metacarpus. The fingers are painful and numb in the most intensive phase of the disease. In the second phase, there is a bruising and swelling, and in the third phase the fingers become very warm and red. Such episodes can be triggered by emotional factors, among others. In the presence of a comorbid mental illness, especially with a strong affective component, the can effectively hinder the therapeutic process. It should be noted that this type of vascular problem cannot be treated only with psychotherapy. Even though it has a psychosomatic effect, it should not be considered as a specific conversion abnormality. During an RD episode, patient should be placed in a warm room and the hands ought to be immersed in warm water. In addition, physical therapy and

the administration of nicotinic acid derivatives can also have a long-term satisfactory effect. Psychotherapy can be beneficial in learning how to regulate the emotional factor and manage stress in an adaptative way.

Are functional disorders and neurovegetative dysfunctions the same?

The key question is, can FD and ADS be treated as one type of disease? It depends on the context of its development and what may have a potentially greater impact on its occurrence: psychogenic background or the progressing organic process. It was indicated that medically unexplained symptoms, which are considered to be functional disorders, may be conditioned by somatization mechanisms. The term somatization can be translated as projecting mental symptoms to somatic abnormalities. The severity of this type of disorder is evident when the patient experiences various types of life difficulties, conflicts or events. Patients do not perceive these dependencies, and when the clinician is trying to explain to them the potential nature of this state, they feel offended and misunderstood. That kind of FD can be effectively treated by psychotherapy, for example short-term psychodynamic psychotherapy (Abbass et al. 2021). Another situation is with neurovegetative dysfunctions or symptoms that may herald a disease of the nervous system. Their evaluation requires a comprehensive medical evaluation and often pharmacotherapeutic support. The patient's condition must be constantly monitored and psychotherapy cannot be considered as a firstline method. However, preventive actions are possible to avert the disease. In this dimension, FD and ADS are not the same diseases.

Overall, the cognitive-behavioral model (CBT) of medically unexplained symptoms has recently been criticized and it is possible that soon this diagnostic unit will meet new research data on its nature (Scott *et al.* 2022). The CBT theory explains development of the FD process as the result of disconcerting beliefs (catastrophic thinking or serious disease convictions) and dysfunctional behaviors (obsessive body attention, avoidant behaviors or excessive health care utilization). Research shows inconclusive results in the effectiveness of CBT in relieving the symptoms of FD (Kroenke and Swindle 2000).

However, autonomic dysfunctions can be caused by regional disorders, which are concentrated on the individual organ, or by generalized

diseases. The latter often affect various organ systems, for instance those involved in blood pressure or thermoregulation. Quite common cardiovascular ADS is orthostatic hypertension and hypotension. Although hypotension does not cause many symptoms, it can be a condition of significant morbidity. One of the potential causes may be the neurovegetative system (mainly sympathetic), and then it is called neurogenic orthostatic hypotension. In this type, the levels of plasma noradrenaline do not rise in an upright position, as in healthy subjects, and it informs about abnormal sympathetic activity. It is possible that this type without progressing organic disease of orthostatic hypotension is related to Pavlov's concept of a weak nervous system. There is a weakness that could include, among other things, the failure of the sympathetic part. Such a case may be associated with an increase in susceptibility to various health problems. Moreover, if such episodes occur before a serious nervous system or organ disease, we can say that this is a specific part of the neurasthenic period (NP) and a neurovegetative dystonia, not FD. In conclusion to this paragraph, it is possible that during the course of functional disorders some symptoms can be transformed (or they may reappear) into ADS (in the case of various favorable conditions), and then, during the NP, into a serious somatic disease.

Symptoms described as functional or psychosomatic may be common in various mental disorders. An example would be depression. Moreover, the autonomic dysfunctions also have been indicated in the depressive disorders as a widespread aliment (Kemp et al. 2012; Licht et al. 2008). Research has shown that heart rate variability (HRV) can be a predictive method for the assessment of prefrontal cortex effectivity in the emotional regulation, psychological plasticity and social engagement (Geisler et al. 2013). Thus, this correlation is supported by the vagus nerve action, which has a key role in the regulation of several allosteric systems and in the inhibition of potential psychosomatic incidents (Thayer and Lane 2009). Functional somatic symptoms in depression can transform into neurovegetative dysfunctions and then, after some time, into a serious organic disorder, for example coronary artery disease and acute cardiovascular sequelae such as hypertension, myocardial infarction and congestive heart failure (Nemeroff and Goldschmidt-Clermont 2012). Therefore, it is very important to monitor somatic symptoms in depression to prevent the development of the disease. For instance, measured lowered HRV is

greatly prognostic for some cardiovascular events such as arrythmias and myocardial infarction. Furthermore, cardiac mortality has a strong association with that parameter (Carney and Freedland 2009; Udupa *et al.* 2007). Therefore, the sensitivity of the autonomic nervous system in depression and related disorders, for instance bipolar disorders (Lee *et al.* 2012), should be included and considered in both psychotherapy and pharmacotherapy or other alternative therapeutic methods (Matraszek-Gawron *et al.* 2019).

Conclusions

Despite many biological explanatory concepts, the nature of functional disorders still remains unclear. Probably the interaction between biological and psychopathological factors could have a key role in somatization processes.

Over the years, the concept of organ neuroses has evolved into neurovegetative dysfunctions. They can be associated with the neurasthenic period prior to disease and can herald serious somatic diseases in susceptible individuals.

Neurocirculatory asthenia and Raynaud's disease are important examples of neurovegetative dysfunctions and can lead to dangerous somatic complications.

The distinction between functional disorders and neurovegetative dysfunctions should be respected as these diseases can have significantly different psychological and somatic consequences.

Neurovegetative dysfunctions are common features in affective or anxiety disorders and should be constantly monitored to prevent the development of cardiovascular complications.

Finally, the proposed distinction between functional disorders and neurovegetative dysfunctions must be assessed by further research. Controlled clinical longitudinal studies, for instance, may have a key role in this investigation.

Disclosure

The authors declare no conflict of interest.

References

- Abbass A, Lumley MA, Town J, et al. Short-term psychodynamic psychotherapy for functional somatic disorders: a systematic review and meta-analysis of within-treatment effects. J Psychosom Res 2021; 145: 110473.
- 2. Bilikiewicz A. Psychiatria kliniczna. PZWL, Warszawa 1979
- 3. Bourke JH, Langford RM, White PD. The common link between functional somatic syndromes may be central sensitization. J Psychosom Res 2015; 78: 228-236.

- Budtz-Lilly A, Fink P, Ørnbøl E, et al. A new questionnaire to identify bodily distress in primary care: the 'BDS checklist'. J Psychosom Res 2015; 78: 536-545.
- Budtz-Lilly A, Schröder A, Rask MT, et al. Bodily distress syndrome: A new diagnosis for functional disorders in primary care? BMC Primary Care 2015; 16: 180.
- Burton C, Fink P, Henningsen P, et al. Functional somatic disorders: discussion paper for a new common classification for research and clinical use. BMC Medicine 2020; 18: 34.
- 7. Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. Cleve Clin J Med 2009; 76 (Suppl 2): S13-S17.
- Czachowski S. Functional disorders new proposals for definition, classifications, etiology and therapies. Psychiatr Pol 2021; 256: 1-10.
- 9. Da Costa JM. On irritable heart. Am J Med Sci 1871; 61: 17-52
- 10. Fava GA, Magelli C, Savron G, et al. Neurocirculatory asthenia: a reassessment using modern psychosomatic criteria. Acta Psychiatr Scand 1994; 89: 314-319.
- 11. Fink P, Schrörder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. J Psychosom Res 2010; 68: 415-426.
- 12. Fink P, Toft T, Hansen MS, et al. Symptoms and syndromes of bodily distress: An exploratory study of 978 internal medical, neurological, and primary care patients. Psychosom Med 2007; 69: 30-39.
- 13. Friston K. The free-energy principle: a rough guide to the brain? Trends Cogn Sci 2009; 13: 293-301.
- 14. Geisler FC, Kubiak T, Siewert K, Weber H. Cardiac vagal tone is associated with social engagement and self-regulation. Biol Psychol 2013; 93: 279-286.
- 15. Haller H, Cramer H, Lauche R, Dobos G. Somatoform disorders and medically unexplained symptoms in primary care. Dtsch Arztebl Int 2015; 112: 279-287.
- 16. Henningsen P. Management of somatic symptom disorder. Dialogues Clin Neurosci 2018; 20: 23-31.
- Henningsen P, Gundel H, Kop WJ, et al. Persistent physical symptoms as a perceptual dysregulation: a neuropsychobehavioral model and its clinical implications. Psychosom Med 2018; 80: 422-431.
- 18. Ivbijaro G, Goldberg D. Bodily distress syndrome (BDS): the evolution from medically unexplained symptoms (MUS). Ment Health Fam Med 2013; 10: 63-64.
- Kemp AH, Quintana DS., Gray MA et al. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PLoS One 2012; 7: e30777.
- Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. Psychother Psychosom 2000; 69: 205-215.
- 21. Lee JS, Kim B, Hong Y, Joo YH. Heart rate variability in the subsyndromal depressive phase of bipolar disorder. Psychiatry Clin Neurosci 2012; 66: 361-366.
- Licht CMM, de Geus EJC, Zitman FG, et al. Association between major depressive disorder and heart rate variability in the Netherlands study of depression and anxiety (NESDA). Arch Gen Psychiatry 2008; 65: 1358-1367.
- 23. Matraszek-Gawron R, Chwil M, Terlecka P, Skoczylas MM. Recent studies on anti-depressant bioactive substances in selected species from the genera hemerocallis and gladiolus: a systematic review. Pharmaceuticals 2019; 12: 172.
- 24. McAndrew LM, Crede M, Maestro K, et al. Using the common-sense model to understand health outcomes

- for medically unexplained symptoms: a meta-analysis. Health Psychol Rev 2018; 13: 427-446.
- 25. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heart-break. The link between depression and cardiovascular disease. Nat Rev Cardiol 2012; 9: 526-539.
- 26. Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain 2019; 160: 28-37.
- Nijs J, Meeus M, Van Oosterwijck J, et al. In the mind or in the brain? Scientific evidence for central sensitization in chronic fatigue syndrome. Eur J Clin Investig 2012; 42: 203-212
- 28. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialties. J Psychosom Res 2001; 51: 361-367.
- 29. Rizzi M, Radovanovic D, Santus P, et al. Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients. Clin Exp Rheumatol 2017; 35: 74-80.
- 30. Russell A, Hepgul N, Nikkheslat N, et al. Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome. Psychoneuroendocrinology 2019; 100: 276-285.
- Scott MJ, Crawford JS, Geraghty KJ, Marks DF. The 'medically unexplained symptoms' syndrome concept and the cognitive-behavioural treatment model. J Health Psychol 2022; 27: 3-8.
- 32. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev 2009; 33: 81-88.
- 33. Tomas C, Newton J. Metabolic abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a mini-review. Biochem Soc Trans 2018; 46: 547-553.
- 34. Udupa K, Sathyaprabha TN, Thirthalli J, et al. Modulation of cardiac autonomic functions in patients with major depression treated with repetitive transcranial magnetic stimulation. J Affect Disord 2007; 104: 231-236.