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Review

# Functional neuroimaging in patients presenting with somatoform disorders: A model for investigating persisting symptoms after tick bites and post-treatment Lyme disease syndrome?

*Neuroimagerie fonctionnelle chez les patients atteints de troubles somatoformes : modèle  
d'investigation des symptômes persistant après une morsure de tique et post-Lyme syndrome ?*

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## Abstract

Approximately 10% of patients presenting with Lyme disease experience fatigue, musculoskeletal pain, concentration disorders, or short-term memory deficits in the six months following treatment. This entity has been defined as post-Lyme disease syndrome or post-treatment Lyme disease syndrome. The pathophysiology of this syndrome is unknown, but neither persistence of the bacterium nor effectiveness of antibiotics are currently reported in the literature. The French High Council for Public Health (French acronym HCSP) has recently defined a new entity called “persistent polymorphic symptoms after a tick bite” allowing for designing studies to better understand these subjective presentations, for which objective biomarkers are currently lacking. This entity encompasses patients experiencing fatigue and generalized pain in the months following a tick bite and can be associated with several subjective symptoms with major impact on the quality of life. In the field of somatoform disorders, this article reviews functional neuroimaging studies in patients presenting with subjective complaints and discusses potential clinical implications for persisting symptoms after tick bites and post-treatment Lyme disease syndrome.

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**Keywords:** Molecular imaging; Chronic Lyme; Fibromyalgia; Conversion disorder; Somatoform disorder

## Résumé

Environ 10 % des patients atteints de maladie de Lyme présentent des symptômes de fatigue, des douleurs musculosquelettiques, des troubles de la concentration ou des troubles de la mémoire à court terme dans les six mois suivant le traitement. Cette entité a été appelée « syndrome post-Lyme » ou « syndrome post-traitement de la maladie de Lyme ». La physiopathologie de ce syndrome reste inconnue, mais ni la persistance de la bactérie ni l'efficacité d'une antibiothérapie n'ont été démontrées dans la littérature. Le Haut Conseil de la santé publique (HCSP) a récemment défini une nouvelle entité, dénommée « sémiologie persistante polymorphe après morsure de tique », permettant ainsi la réalisation d'études visant à mieux comprendre ces présentations subjectives pour lesquelles aucun marqueur biologique objectif n'est actuellement disponible. Cette entité

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englobe les patients présentant des symptômes de fatigue et des douleurs généralisées dans les mois suivant une morsure de tique, qui peuvent être associés à plusieurs symptômes subjectifs ayant un impact considérable sur la qualité de vie. Dans le domaine des troubles somatoformes, cet article examine les études de neuroimagerie réalisées chez des patients présentant des symptômes subjectifs et évoque les implications cliniques éventuelles pour les symptômes persistant après morsure de tique ainsi que pour le syndrome post-traitement de la maladie de Lyme.

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*Mots clés* : Imagerie moléculaire ; Lyme chronique ; Fibromyalgie ; Trouble dissociatif ; Trouble somatoforme

## 1. Introduction

Complaints, symptoms, and diseases are difficult to manage in the absence of causal pathophysiological substrate and related biomarkers that can be identified at the individual level. They are consequently associated with doctor hopping, unnecessary costs for health systems, and alteration of the patient's quality of life [1]. Objective biomarkers are helpful for the medical recognition of the subject as a patient and for the medical recognition of subjective complaints as part of a disease to be supported by health insurance. These biomarkers also contribute to better understanding the associated pathophysiology. This is an essential step for healthcare improvement provided by early diagnosis and better prognosis, as well as for guiding and evaluating treatments [2].

Lyme disease is a complex infection with a number of well-known objective clinical presentations. Conventional antibiotics are effective against all types of presentations [3]. However, approximately 10% of patients develop fatigue, musculoskeletal pain, concentration disorders, or deficits in short-term memory within six months after treatment. This entity has been defined as post-Lyme disease syndrome (PLDS) or post-treatment Lyme disease syndrome (PTLDS). The pathophysiology is unknown, but neither the persistence of the bacterium nor the effectiveness of antibiotics is currently reported in the literature [4].

Some physicians and patients' associations advocate a "chronic Lyme disease", which they believe to be due to the chronic and undetectable persistence of *Borrelia*. This entity is increasingly used in North America and Europe as a diagnosis for patients presenting with a myriad of subjective symptoms such as pain, fatigue, neurocognitive deficits – with or without a positive serology for Lyme disease. However, there is no current reproducible and convincing evidence of a relation with *Borrelia burgdorferi* sensu lato infection [3]. Consequently, the diagnosis is often based solely on clinical judgement rather than on validated laboratory assays or even clinical criteria. H.M. Feder recently identified four categories of patients in the "chronic Lyme disease" group [3]. The first was composed of patients presenting with subjective symptoms and no evidence of *Borrelia* infection. The second category of patients had a well-defined differential diagnosis (e.g., multiple sclerosis or autoimmune diseases) that could also explain the symptoms attributed to Lyme disease. Patients of the third category had a positive serology for Lyme disease and symptoms of unknown origin but with no history of symptoms compatible with Lyme disease. The last category corresponded to PTLDS.

The French High Council for Public Health (French acronym HCSP) has recently defined a new entity, allowing to design studies to better understand these categories mainly composed of subjective presentations, and for which we currently lack objective biomarkers [5]. This entity is called "persistent polymorphic symptoms after a tick bite" (PPSTB). It encompasses patients presenting with fatigue and generalized pain in the months following a tick bite and can be associated with several subjective symptoms with major impact on the quality of life.

In the field of somatoform disorders, this article reviews functional neuroimaging studies of patients presenting with subjective complaints and discusses potential clinical implications for PPSTB/PTLDS.

## 2. "Somatoform disorders" and "somatic symptoms and related disorders"

In the fourth edition of the Diagnostic and statistical manual of mental disorders (DSM-IV<sup>TM</sup>), patients presenting with physical symptoms that are not fully explained by a medical condition, are considered as presenting with a somatoform disorder [6]. However, the main characteristics of these patients is not physical symptoms per se, but instead the way they present and interpret them as well as the significant distress and impairment they exhibit in response to their symptoms. The concept of somatoform disorder has therefore been criticized, because it overemphasized the lack of medical explanation. Furthermore, due to this absence of medical explanation, individuals regarded this diagnosis as derogatory and demeaning, implying that their physical symptoms were not "real" or worst "hysterical". This is the reason why, in the fifth edition of the Diagnostic and statistical manual of mental disorders (DSM-5<sup>TM</sup>) [7], the category of "somatoform disorders" has been replaced by that of "somatic symptoms and related disorders". The common features of this category are the presence of somatic symptoms plus abnormal thoughts, feelings, or behaviors in response to symptoms. Interestingly, due to the presence of such abnormal thoughts, feelings or behaviors, the authors of DSM-5<sup>TM</sup> considered that somatic symptom disorders may also be associated with diagnosed medical disorders.

However, a direct causal relationship is not necessarily present between diagnosed medical disorders and somatic symptom disorders, and they do not necessarily pertain to the same disorder. The presence of a previous medical condition is just considered a possible contributing factor to the development of a somatic symptom disorder [7]. This is particularly important to bear in mind as individuals presenting with somatic symptom

disorders are commonly encountered in primary care and other medical settings, but less commonly in psychiatric and other mental health settings [7]. These patients may have multiple somatic symptoms, although sometimes only one severe symptom, most commonly pain, is present. Symptoms may be specific (e.g., localized anesthesia) or relatively unspecific (e.g., fatigue). These clinical characteristics are associated with persistent thoughts about symptom severity, high level of anxiety about illness, excessive time and energy devoted to health concern, but sometimes only with a “belle indifférence” syndrome.

In the DSM-5<sup>TM</sup>, the chapter on “somatic symptoms and related disorders” includes the following disorders: somatic symptom disorder, illness anxiety disorder, conversion disorder, psychological factors affecting other medical conditions, factitious disorder, other somatic symptoms and related disorders, and unspecified somatic symptoms and related disorders. Conversion disorders are probably the most popular and the most studied of these disorders. While they have been reported as a focus of treatment in 1–3% of outpatient referrals to mental health clinics, they are associated with a prevalence of 1–10% in medicine or surgery departments and up to 30% in neurology departments [8]. Conversion disorder is considered a functional central nervous system disorder. It is not caused by a neurological injury or a general medical condition [9]. It is characterized by the presence of non-simulated neurological symptoms or deficits affecting voluntary motor or sensory functions and often associated with dissociative symptoms such as depersonalization, derealization, and dissociative amnesia, particularly at symptom onset or during attacks. The non-validation of the disease as “organic” does not invalidate the disease per se [10]. Clinical findings usually show clear evidence of incompatibility with organic disease. Internal consistency at examination may demonstrate incompatibility [7]. Nevertheless, the presence of previous organic diseases causing similar symptoms is a typical risk factor, and the disability severity can be similar to that experienced by patients presenting with comparable medical illnesses. Other risk factors include maladaptive personality traits, a history of childhood abuse and neglect, and the presence of stress or trauma, either psychological or physical in nature at disease onset [7].

According to contemporary dissociation theory, conversion symptoms are generated preconsciously by an attentional gating mechanism: they are deemed to reflect a distortion in awareness resulting from information “stuck” in the cognitive system. This inappropriate information has been called rogue representation or prior belief [11]. When the patient attempts to control cognition or action, the attempt is unsuccessful because the locus of patient’s deficit is the chronic activation and selection of rogue representation. According to this approach, conversion symptoms constitute an alteration in the body image generated by information in the cognitive system, rather than disturbances in the neural hardware itself. Patients often have a history of physical illness; thus suggesting that many rogue representations arise out of memory traces acquired during episodes of organic pathology. The physical components of emotional states also leave representations in memory that could provide the basis for the later development of conversion symptoms.

Traumatic experiences such as physical or sexual abuse provide one of the richest sources of material for the development of rogue representations. One example may be the sensorimotor components of some defensive reactions that occur in response to traumatic events. Other sources include indirect exposure to other people’s trauma, the sociocultural transmission of information about health and illness, and direct and verbal suggestion [11].

### 3. Functional imaging as a biomarker of subjective complaints?

Development of biomarkers are often driven by advances in medical imaging [2]. More specifically, functional imaging could have a pivotal role in the absence of detected lesions. For complaints or symptoms currently perceived as purely functional and for early-stage diseases associated with delayed lesions only, functional imaging provides more sensitive tools. Among them, functional MRI (fMRI) based on blood-oxygen-level dependent (BOLD) contrast is an increasingly available method for the research study of brain activity, at rest or during a paradigm of activation, among patients presenting with neurological and psychiatric disorders. fMRI and BOLD are also available in current clinical practice, mostly for presurgical planning in patients presenting with a lesion adjacent to a critically functional brain region [12]. On the other hand, PET and SPECT imaging contribute to identifying molecular signature, usually at resting state, through the targeting of biological processes by specific tracers radiomarked as radiopharmaceuticals [13]. The radioactive labelling provides optimal sensitivity with subpicomolar detection after the introduction of very small amount of tracer that does not disrupt the molecular environment. Amyloidopathy can for instance be detected with PET imaging at least 15 years before cognitive deficits in Alzheimer’s disease [14]; 50% of dopaminergic loss is identified with SPECT imaging at the early diagnosis of Parkinson’s disease [15], and a frontotemporal dysfunction is identified in case of depression [16]. Among the various molecular targets, those related to cerebral blood flow (mainly with SPECT) and metabolic rate of glucose (PET with FDG, fluorodeoxyglucose) are the most studied and validated at the individual level. These two molecular processes are correlated, reflecting the brain energetic need to maintain synaptic activity through the neurovascular coupling [17], and have been widely used to explore functional and psychiatric diseases with high sensitivity. International clinical recommendations are available for the evaluation of cognitive complaints associated with traumatic brain injury, and in psychiatric diseases for the differential diagnosis and follow-up of depression [18]. SPECT has for instance shown perfusion abnormalities in traumatic brain injuries despite normal morphology, and results are considered to have a prognostic value for persistence of neuropsychological sequelae [19]. Besides these recommendations, research studies in functional imaging of patients with subjective complaints mostly focus on somatoform disorders, conversion disorders, fibromyalgia, and macrophagic myofasciitis.

#### 4. Functional neuroimaging abnormalities in somatic symptom disorders

Functional neuroimaging of patients with somatic symptoms and conversion disorders suggests brain changes distinct from those of people simulating symptoms or those of healthy controls [20]. These studies support the hypothesis of a specific alteration in emotion processing that triggers a large variety of symptoms through dysregulation of specific motor or sensory systems.

Selective reductions have been reported in the activity of frontal and subcortical circuits involved in motor control during hysterical paralysis, of somatosensory cortices during hysterical anesthesia, and of visual cortex during hysterical blindness. Concomitantly, increased activation is observed in limbic regions during conversion symptoms affecting various sensory or motor modalities. Taken together, this data usually does not support previous views sustaining that hysteria might involve an exclusion of sensorimotor representations, from awareness to attentional processes. They rather seem to point to a modulation of such representations by primary affective or stress-related factors, perhaps involving primitive reflexive mechanisms of protection and alertness that are partly independent of conscious control and mediated by dynamic modulatory interactions between limbic and sensorimotor networks. Motor conversion symptoms have been characterized by the concomitant dysfunction of the following brain regions [9]:

- salience network (amygdala, insula, and cingulate cortices) connected with motor regions through supplementary motor area;
- prefrontal regions involved in behavioral control;
- ventromedial prefrontal cortex (vmPFC) regions that support self-monitoring and information processing about internal body states and environment;
- self-agency network and regions involved in memory suppression.

It was hypothesized that these dysfunctional brain networks may alter the selection of motor patterns through the influence of the supplementary motor area and the dorsolateral prefrontal cortex which are critical “hubs” connecting affective networks with regions underpinning motor control.

This may result in deficient processing of either motor intention or disruption between motor intention and motor execution. Furthermore, an overactive self-monitoring with enhanced limbic neural activity, which interferes with movement planning, and initiation within frontal regions could contribute to disrupt motor execution [21]. The dysregulation of brain networks related to the processing of emotions may also affect the integration of complex sensory inputs and lead to functional sensory symptoms. Similar brain regions are involved in both positive and negative conversion symptoms, but differences focus on the nature of functional alterations (i.e., increased or decreased activity). Interestingly, hypnosis and conversion might share common neurophysiological mechanisms, with similar PET activations in hypnotic paralysis and conversion

hysteria [22] and with interactions between emotional regions and the motor/sensory systems.

#### 5. Functional neuroimaging abnormalities in fibromyalgia and macrophagic myofasciitis

Fibromyalgia syndrome is a chronic pain condition characterized by widespread musculoskeletal aches, pain and stiffness, soft tissue tenderness, general fatigue, and sleep disturbances, without any clinically demonstrable peripheral nociceptive cause [23]. Although a psychogenic cause was initially postulated, fMRI activation studies demonstrated global dysfunction of central pain processing, supporting the hypothesis of central sensitization [24]. Similar painful pressure applied in patients and in controls did not result in activation of any common cerebral areas and showed greater effects in patients. On the other hand, similar brain patterns are obtained for the same intensity of provoked pain, and for lower stimuli in patients versus healthy subjects. Interestingly, these functional abnormalities have also been reported at resting state at the individual level in the absence of provoked pain, in hyperalgesia patients presenting with fibromyalgia using SPECT imaging [25]. These abnormalities could be related to the metabolism of adenosine [26]. Hyperperfusion regions were observed in primary somatosensory cortices, in regions of the brain known to be involved in the sensory dimension of pain processing, while hypoperfusion regions were found in frontal, cingulate, medial temporal, and cerebellar cortices, in areas assumed to be associated with the affective-attentional dimension of pain. Interestingly, these abnormalities were correlated with the alteration of quality of life as subjectively evaluated by patients’ reports [27]. Moreover, asymmetrical symptoms were associated with asymmetrical functional abnormalities [28]. As current pharmacological and non-pharmacological therapies act differently on the various components of pain, functional neuroimaging could be a valuable and readily available tool to guide individual therapeutic strategy and to provide objective follow-up of pain processing recovery on treatment [29]. The relation with predictive response and follow-up of recovery has been described with ketamine, transcranial magnetic stimulation, and hyperbaric oxygen therapy [30–33].

Macrophagic myofasciitis is a controversial condition associated with anatomopathological findings. A peculiar FDG-PET pattern has been reported with hypometabolisms involving the occipitotemporal cortex and cerebellum [34] and with perfusion SPECT [35]. These patterns have been reported to be associated with distinct cognitive profiles [35]. Interestingly, the individual classification approach showed very high level of performance to distinguish between patients and healthy subjects, suggesting a potential diagnostic value [36].

#### 6. Functional neuroimaging abnormalities in Lyme disease

Little data has been reported on functional brain imaging in patients presenting with subjective symptoms attributed to Lyme disease. Newberg et al. assessed 23 patients with a

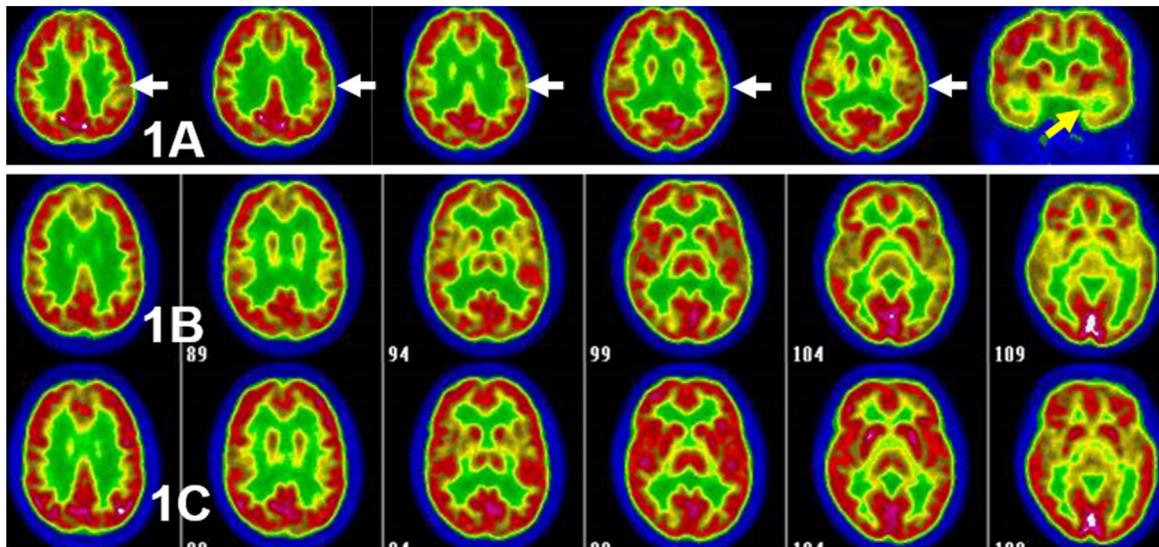


Fig. 1. FDG-PET slices of two recent patients explored at resting state for subjective complaints. A (first patient): axial and coronal slices show left moderate hypometabolism of the amygdala (yellow arrow) and slight hypometabolism of the central region (white arrows). B (second patient): axial slices with diffuse cortical moderate hypometabolism, normalized in C after treatment by doxycycline and hydroxychloroquine.

*Coupes TEP-FDG de deux patients récemment évalués au repos pour symptômes subjectifs. A (premier patient) : coupes axiales et coronales montrant un hypométabolisme modéré gauche de l'amygdale (flèche jaune) et un léger hypométabolisme de la région centrale (flèches blanches). B (second patient) : coupes axiales montrant un hypométabolisme cortical diffus modéré, normalisé en C après traitement par doxycycline et hydroxychloroquine.*

positive serology for Lyme disease (the serological method and titers were not described) presenting with cognitive disorder, visual disturbances, and fatigue. They reported FDG-PET temporal hypometabolism in 74% of patients at resting state, possibly in line with memory deficits [37]. Seven of these patients had diffuse cortical hypometabolism that included the frontal and parietal lobes. Donta et al. performed brain SPECT imaging in 183 patients defined as having “chronic Lyme disease”, with negative and positive serologies and mainly subjective symptoms [38]. The authors identified abnormalities in 75% of them. Interestingly, the antibiotic therapy resulted in resolution or improvement of abnormalities in 70% of patients over a 1- to 2-year period.

### 7. Clinical cases of the use of FDG-PET imaging in patients with subjective complaints

FDG-PET used in clinical practice may allow for resolving a number of problems of psychogenic or organic origins. One of the authors of the present article once had patients presenting with a suspicion of cerebral Whipple disease without identification of pathogen, because this infection can have cerebral presentations without peripheral localization (unpublished personal report).

A cerebral FDG-PET was performed at rest in two patients. The first patient was a 40-year-old woman presenting with a non-organic hemiplegia. The FDG-PET was typical of this pathology with a slight diminution of frontal and amygdala metabolism on the opposite side of the hemiplegia (Fig. 1A). The visualization of this image made her feel recognized as a patient, and no longer classified as “not sick” or as a “simulating” person.

The second patient was a 35-year-old woman, who had a peculiar emotive context complicating her symptom

assessment. She presented with a generalized cerebral moderate hypometabolism (Fig. 1B) as can be observed in cerebral Whipple disease [39]. As a therapeutic test, doxycycline and hydroxychloroquine treatment was introduced and surprisingly, after six months of treatment, cerebral metabolism was entirely restored (Fig. 1C), and was comparable to any other people of her age.

Cerebral FDG-PET performed in both patients contributed to the diagnosis and to a clinically and metabolically efficient empirical treatment initiation in the second patient.

### 8. Perspectives: therapeutic implications

Current conceptions of somatoform disorders, reinforced by the findings of neuroimaging studies, have led to the use of novel therapeutic approaches. Two recent systematic reviews [21,40] showed that non-invasive brain stimulation techniques, including electroconvulsive therapy (ECT) and mainly repetitive transcranial magnetic stimulation (rTMS), improved conversion symptoms, as demonstrated for rTMS and depression [16,41–49] or fibromyalgia [32] in line with neuroimaging biomarkers. In the studies included in these reviews, it was found that the stimulation of the motor cortex contralateral to the corresponding paralysis was able to restore the motor function in somatoform disorders. In some cases [21,50], the associated sensory symptoms improved as well. In accordance with the results of neuroimaging studies, it was hypothesized that rTMS could enhance or substitute an insufficient input to the motor cortex from failing frontal executive areas, and thereby open the way to the learning process that leads to the reacquisition of limb use [51]. Furthermore, as rTMS induces noticeable involuntary contractions, these effects may allow patients to become aware of the possibility of movement and thus of the integrity of the

motor pathways [21]. This could contribute to correct patient's rogue representation and lead to a change in prior belief [40].

The question as to whether complementary stimulations in other cortical regions than the primary cortex could enhance therapeutic efficacy of rTMS remains open. It has been suggested, in case of functional blindness, that the experience of phosphenes during visual cortex stimulation may act in an analogous manner to experiencing the movement of a "paretic" limb in re-establishing normal function [40]. In a more theoretical vein, brain stimulation techniques are likely to be used to correct the functional abnormalities in central networks that may be involved in the pathophysiology of somatoform disorders.

Interestingly, recent findings agree with the three assumptions supporting the new classification framework project launched by the National Institute of Mental health (NIMH) for research on mental disorders [52]. First, mental disorders are brain disorders but, unlike neurological disorders with identifiable lesions, they can be addressed as disorders of brain circuits. Second, the dysfunction in neural circuits can be identified with clinical neuroscience tools. Third, data from clinical neuroscience will yield biosignatures correlated with clinical symptoms for better clinical management.

Many of the clinical manifestations exhibited by patients with persisting symptoms after tick bites and/or post-treatment Lyme disease syndrome are also observed in those with somatic symptoms and related disorders, including conversion disorders. Furthermore, either tick bites, Lyme disease, or the sociocultural transmission of information about them may favor, as previously shown, the development of somatic symptom disorders in at-risk individuals. It may thus be crucial to correctly identify patients presenting with these disorders whose symptoms were previously considered as unexplained. In this regard, patients' attitudes, thoughts, feelings, or behaviors may be of help. Modern brain imaging may even provide specific evidence. The correct identification of these patients may provide more specific therapeutic approaches, on the basis of functional neuroimaging. Consequently, there is an urgent need to conduct neuroimaging research in patients presenting with persisting symptoms after tick bites and/or post-treatment Lyme disease.

It is the psychiatrists' hope that we may enter a time in which even "hysterical" patients could benefit from progress in neurosciences. Aren't infectious disease specialists sharing the same hope for their "chronic Lyme disease" patients?

## Disclosure of interest

The authors declare that they have no competing interest.

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