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

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Abstract

Approximately 10% of patients with Lyme disease will develop fatigue, musculoskeletal pain, difficulties of concentration or deficits in short-term memory within the 6 months after treatment. This entity has been defined as Post Lyme Disease Syndrome or Post Treatment Lyme Disease Syndrome. The pathophysiology of this syndrome is not known, but neither persistence of the bacterium nor efficiency of antibiotics are currently sustained by the existing literature. In France, the *Haut Conseil de Santé Publique* has recently define a new entity called "persistent polymorphic semiology after tick bite" allowing to design studies to better understand these subjective manifestations, for which objective biomarkers currently lack. This entity encompasses patients suffering from fatigue and global pain in the months following a tick bite, and can be associated to several subjective symptoms with a major impact on quality of life.

In interaction with the model of somatoform disorders, this article proposes a review of functional neuroimaging studies in patients with subjective complaints and discusses possible clinical implications for persisting symptoms after tick bites and Post Treatment Lyme Disease Syndrome.

Key words: Molecular Imaging, PET, SPECT, fMRI, Chronic Lyme, Fibromyalgia, Conversion Disorder, Somatoform Disorder

Introduction

In the absence of causal pathophysiological substrate and related biomarkers identifiable at individual level, complaints, symptoms and diseases are difficult to care, and consequently associated with medical nomadism, unnecessary costs for health systems and alteration of quality of life for patients [1]. In this line, objective biomarkers are helpful for the medical recognition of the subject as a patient, and subjective complaints as part of a disease to be supported by health policy. These biomarkers also contribute to better understand the associated pathophysiology which is an essential step of healthcare improvement through the determination of early diagnosis and prognosis, as well as the orientation and evaluation of therapeutics [2]

Lyme disease is a complex infection with a number of well-known objective clinical manifestations. All of them respond well to conventional antibiotics [3]. However, approximately 10% of patients will develop fatigue, musculoskeletal pain, difficulties of concentration or deficits in short-term memory within the 6 months after treatment. This entity has been defined as Post Lyme Disease Syndrome (PLDS) or Post Treatment Lyme Disease Syndrome (PTLDS). The pathophysiology is not known, but neither persistence of the bacterium nor efficiency of antibiotics are currently sustained by the existing literature [4].

Besides this syndrome, some medical doctors and patients' associations advocate a "chronic Lyme disease", which they believe to be due to chronic 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, and this with or without positive serology for Lyme disease. However, there is no current reproducible and convincing evidence of any relationship to *Borrelia burgdorferi sensu lato* infection. Consequently, the diagnosis is often based solely on the clinical judgement rather than on validated laboratory assays or even clinical criteria. In a recent work, H.M. Feder

identified four categories of patients in the "chronic Lyme" group [3]. The first was composed of patients 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 cause but with no compatible history of symptoms compatible with Lyme disease. The last category corresponds to PTLDS.

In France, the *Haut Conseil de Santé Publique* has recently define a new entity allowing to design studies to better understand these categories mainly composed of subjective manifestations, and for which we currently lack objective biomarkers [5]. This entity is called "persistent polymorphic semiology after tick bite" (PPSTB). It encompasses patients suffering from fatigue and global pain in the months following a tick bite, and can be associated to several subjective symptoms with a major impact on their quality of life.

In interaction with the model of somatoform disorders, this article proposes a review of functional neuroimaging studies in patients with subjective complaints and discusses possible clinical implications for PPSTB/PTLDS.

The model of "somatoform disorders" and "somatic symptoms & related disorders"

In the fourth edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-IV^{TM}), patients presenting with physical symptoms that were not fully explained by a medical condition, were considered as suffering from 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 pejorative 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^{TM}) [7] the category of "somatoform disorder" has been replaced by that of "somatic symptom and related disorder", the common features of which is the presence of somatic symptoms plus abnormal thoughts, feelings, or behaviors in response to their symptoms. Interestingly, due to the presence of such abnormal thoughts, feelings or behaviors, the authors of DSM-5^{TM} consider that somatic symptom disorders can also accompany diagnosed medical disorders.

However, that does not mean that there should be a direct causal relationship between the latter and the former, or that they both pertain to the same disorder. The presence of a previous medical condition is just considered as a possible contributing factor to the development of a somatic symptom disorder [7]. This is particularly important to bear in mind, as individuals with somatic symptom disorders are commonly encountered in primary care and other medical settings, but are less commonly encountered 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 the seriousness of symptoms, high level of anxiety about illness, excessive time and energy devoted to health concern, but sometimes only with a « belle indifference ».

In the DSM-5^{TM}, the chapter on "somatic symptom and related disorders" precisely includes the following disorders: somatic symptom disorder, illness anxiety disorder, conversion disorder (CD), psychological factors affecting other medical conditions, factitious disorder, other somatic symptom and related disorder and unspecified somatic symptom and related disorder. CD is probably the most popular and the most studied among these disorders.

Whereas it has been reported as a focus of treatment in 1-3% of outpatient referrals to mental health clinics, it shows a prevalence of 1-10% in medicine or surgery department, and up to 30% in neurology department [8]. CD is considered as a functional central nervous system disorder, not caused by a neurological injury or a general medical condition [9] 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. Importantly, not validating the disease as « organic » does not invalidate the « disease » as well [10]. Clinical findings usually show clear evidence of incompatibility with organic disease. Internal consistency at examination is one way to demonstrate incompatibility [7]. Nevertheless, the presence of a previous organic disease that causes similar symptoms is a classical risk factor, and the severity of the disability can be similar to that experienced by patients with comparable medical illnesses. Other risk factors comprise maladaptive personality traits, an history of childhood abuse and neglect, and the presence of stress or trauma, either psychological of 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 that has been « 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. The fact that patients often have a history of physical illness suggests 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 certain defensive reactions that occur in response to traumatic events. Other sources include indirect exposure to physical states in others, the sociocultural transmission of information about health and illness, and direct and verbal suggestion [11].

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 assume a pivotal role in absence of detected lesion. For complaints or symptoms currently perceived as purely functional, as well as for early-stage diseases associated with only delayed lesions, functional imaging indeed 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 with neurological and psychiatric disorders, and in current clinical practice mostly for presurgical planning in patients presenting with a lesion close to a critically functional brain region [12]. On the other hand, PET and SPECT imaging contribute to identify molecular signature, usually at resting-state, through the targeting of biological processes by specific tracers radiomarked as radiopharmaceuticals [13]. The radioactive labelling provides optimal sensibility performance with sub-picomolar detection after the introduction of very small amount of tracer that not disrupts the molecular environment. In this line, amyloïdopathy is for example detectable 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 fronto-

temporal dysfunction is identified in depression [16]. Among the various molecular targets, those related to cerebral blood flow (mainly with SPECT) and metabolic rate of glucose (PET with FDG, fluoro-deoxyglucose) are the most studied and validated at individual level. These two molecular processes are linked together, 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 a high sensitivity. In this line, international clinical recommendations exist for the evaluation of cognitive complaints associated with traumatic brain injury, as well as in psychiatric diseases for differential diagnosis and the follow-up of depression [18]. SPECT has for example shown perfusion abnormalities in TBI 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 concern somatoform disorders and CD, and also fibromyalgia and macrophagic myofasciitis.

Functional neuroimaging abnormalities in somatic symptom disorders

In patients with somatic symptom and conversion disorders, functional neuroimaging suggests brain changes distinct from feigning or healthy controls (for review [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.

In details, 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 anaesthesia, and of visual cortex during hysterical blindness. Concomitantly, increased activation is found in limbic regions during conversion symptoms affecting different sensory or motor modalities. Taken together, these data generally do not support previous view that hysteria might involve an exclusion of sensorimotor representations

from awareness through 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. In this line, motor conversion symptoms have been characterized by the concomitant dysfunction of the following brain regions [9]: (i) salience network (amygdala, insula and cingulate cortices) that is connected with motor regions through supplementary motor area, (ii) prefrontal regions involved in behavioural control, (iii) ventromedial prefrontal cortex (vmPFC) regions that support self-monitoring and information processing about internal body states and environment, and (iv) 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 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 concern the nature of the 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], with interactions between emotional regions and the motor/sensory systems.

Functional neuroimaging abnormalities in Fibromyalgia and Macrophagic Myofasciitis

Fibromyalgia syndrome is a chronic pain condition characterised by widespread musculoskeletal aches, pain and stiffness, soft tissue tenderness, general fatigue and sleep disturbances, without a clinically demonstrable peripheral nociceptive cause [23]. Although a psychogenic cause was initially postulated, fMRI activation studies have demonstrated global dysfunction of central pain processing, consolidating the hypothesis of central sensitisation [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 a same intensity of provoked pain, obtained for lower stimuli in patients in comparison to healthy subjects. Interestingly, these functional abnormalities have been also reported at resting-state at individual-level in absence of provoked pain, in hyperalgesic patients with fibromyalgia using SPECT imaging [25]. These abnormalities could be related to metabolism of adenosine [26]. In details, hyperperfusions were found in primary somato-sensory cortices, in regions of the brain known to be involved in the sensory dimension of pain processing, while hypoperfusions were found in frontal, cingulate, medial temporal and cerebellar cortices, in areas assumed to be associated with the affective-attentional dimension of the 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 different components of pain, functional neuroimaging could be a valuable and readily available tool to guide individual therapeutic strategy and provide objective follow-up of pain processing recovery under treatment [29]. In this line, relationship with predictive response and follow-up of the recovery have been described with ketamine, transcranial magnetic stimulation, and hyperbaric oxygen therapy [30–33].

On the other hand, macrophagic myofasciitis is a controversial condition associated with myopathological alterations. A peculiar FDG-PET pattern has been reported with hypometabolisms involving occipito-temporal cortex and cerebellum [34], and also described with perfusion SPECT [35]. These patterns have been reported to be associated with distinct cognitive profiles [35]. Interestingly, individual classification approach showed very high level of performance to distinguish between patients and healthy subjects, suggesting possible diagnostic value [36].

Functional neuroimaging abnormalities in Lyme disease

Few data have been reported concerning functional brain imaging in patients with subjective symptoms attributed to Lyme disease. Newberg et al. have studied 23 patients with a positive serology for Lyme disease (the serological method and titers were not described) suffering from cognitive disorder, visual disturbances and fatigue. They described FDG-PET temporal hypometabolism in 74% of patients at resting-state, possibly in line with memory deficits [37]. Seven of the patients with temporal lobe hypometabolism had diffuse cortical hypometabolism that included the frontal and parietal lobes. Donta *et al.* studied with brain SPECT, 183 patients defined as "chronic Lyme disease", with negative and positive serologies and mainly subjective symptoms [38]. The authors identified abnormalities in 75% of them. Interestingly, antibiotherapy resulted in resolution or improvement of abnormalities in 70% of patients over a 1- to 2-year period.

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

In clinical practice, it is possible that FDG-PET will allow resolving a number of problems linked to psychogenic or organic origins. For example, it has recently been the case

in the consultation of one of us (DR), for suspicion of cerebral Whipple disease without identification of pathogen, because this infection can have cerebral manifestations without peripheric localization.

A cerebral FDG-PET has been performed at resting-state in two patients. The first one was a 40-year old woman presenting a non-organic hemiplegia and the FDG-PET was typical of this pathology with a slight diminution of frontal and amygdala metabolism on the opposite side of the hemiplegia (Figure 1A). The visualization of this image allowing her to feel recognized as a patient, and not any more classified as an “unsick” or “simulating” person.

The second patient was a 35-year-old woman, who had a peculiar emotive context that made difficult the assessment of her symptoms. She showed a generalized cerebral moderate hypometabolism (Figure 1B) as can be observed in cerebral Whipple disease [39]. As a therapeutic test, doxycycline and plaquenil treatment has been introduced and surprisingly, after six months of treatment, cerebral metabolism was entirely restored (Figure 1C), and was comparable to any other people of her age.

In these two cases, cerebral FDG-PET allowed orientation of the diagnosis and in the second case, it allowed an empirical treatment that was efficient clinically and metabolically.

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] have shown that non-invasive brain stimulation techniques, including electro-convulsive therapy (ECT) and mainly repetitive transcranial magnetic stimulation (rTMS) were liable to improve conversion symptoms, as also showed for rTMS with 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 lead to the reacquisition of limb use [51]. Furthermore, as rTMS induces noticeable involuntary contractions, these effects may allow the 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 proposed, 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 [15]. In a more theoretical vein, brain stimulation techniques are likely to be used in order to correct the functional abnormalities in central networks that may be involved in the pathophysiology of somatoform disorders.

Interestingly, recent findings are in line with the three assumptions that support the new classification framework project launched by National Institute of Mental health (NIMH) for research on mental disorders [52]. First, mental disorders are brain disorders but, in contrast to neurological disorders with identifiable lesions, they can be addressed as disorders of brain circuits. Second, the dysfunction in neural circuits can be identified with the tools of clinical neuroscience. Third, data from clinical neuroscience will yield biosignatures that will augment clinical symptoms for 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 encountered in those with somatic symptom and related disorders, including CD. 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 individuals at risk. It may be therefore crucial to correctly identify patients with these disorders whose symptoms were previously considered as unexplained. In this regard patients' attitudes, thoughts, feelings or behaviors may be of help. But even more, the specific patterns that modern brain imagery is able to evidence. The correct identification of these patients may allow to provide more specific therapeutic approaches, on the basis of functional neuroimaging. Consequently, there is an urgent need to conduct neuroimaging research in patients 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 "hysteria" patients could benefit from progress in Neurosciences. Aren't infectiologists sharing the same hope for their "chronic Lyme" patients?

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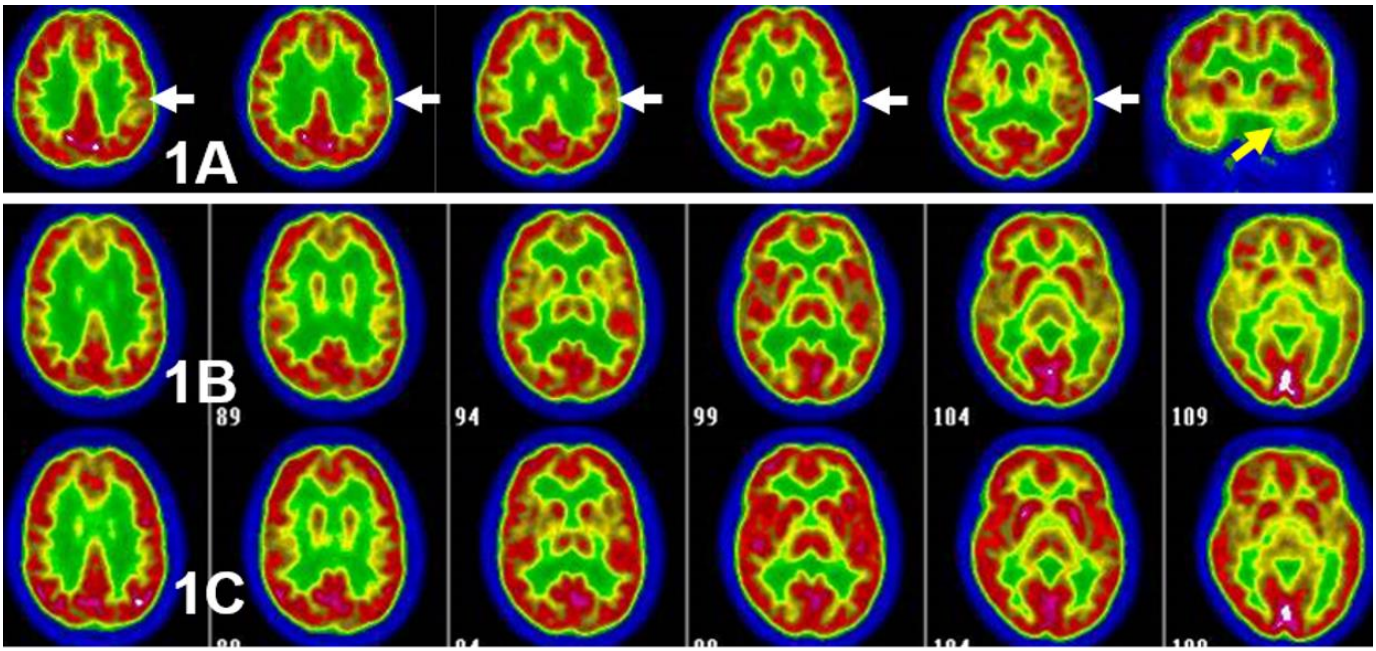
Figure 1



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