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Brain-heart Interactions in Fibromyalgia Syndrome

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The brain and the heart relationship has been a topic for controversy for centuries. Especially in the field of emotions, where the heart seemed (for a long time) to play a prominent role. However, time and science ultimately told us the true story: the brain is indeed the controller of body's movements, behaviors, and emotions. Although, it does all the work through a set of interactions with complex and diverse physiological systems and prominent organs in a homeostatic manner (Ivanov, 2021). In this context, the brain neural networks and the heart interact collaboratively to maintain homeostasis. When this collaboration is deranged, pathological processes take place, which can result in ultimate organ failure. Research has documented some alterations in brain-heart interaction. One of them, the imbalance between overactive sympathetic and decreased parasympathetic neurotransmission, may result in structural and functional changes in central neural circuits and peripheral sensory nerves that may result in cardiac dysfunction and poor prognosis (Fujiu and Manabe, 2022). That relationship can also be bidirectional. In this case, the cardiac alterations may lead to neural remodeling and changes in neurotransmitters and neuropeptides release from autonomic nerves, a process that is likely mediated by neurotrophins and inflammatory cytokines, though genetics may have an influence (Fujiu, 2023). Hence, the interaction between brain and heart is of clinical relevance to understand the mechanisms that maintains body homeostasis and to understand the consequences of the breakage of this interaction to the etiology and maintenance of chronic diseases such as fibromyalgia syndrome (FMS).

To understand the role of impaired brain-heart interaction in FMS and other conditions, some metrics must be used. Different techniques have been used, such as neuroimaging, molecular and single-cell phenotyping, animal models, etc. However, one of these metrics has now reached a sound level of reliability, namely, the heart rate variability (HRV). HRV refers to the fluctuations in the heart rates and in the interval between them that is measurable through electrocardiogram. This metric is sensible to centrally generated brainstem rhythms, baroreceptor influences, and autonomic input. It can also be influenced by behavioral approaches, like exercise and emotions, making HRV also a metric for autonomic modulation (Staud, 2008). Let us discuss what is known about HRV in FMS and how it may be used to understand the complex interplay between the brain and the heart in this health condition.

HRV dysfunction in FMS

HRV is a biomarker of adaptive response to acute and chronic stressors and so, it can present short or long-term alterations. In pathological situations it is expected to be reduced. This reduction is likely caused by an imbalance in the autonomic nervous system. Dysautonomia has been documented in FMS, in which individuals show an overactive sympathetic response during rest but hypoactivity during physically and mentally demanding situations, such as during physical exercise (Zetterman et al., 2023). This impaired response is subjacent to marked clinical symptoms such as orthostatic intolerance, cold extremities, faintness, and non-refreshing sleep. HRV is sensitive to the autonomic imbalance in FMS, in which metrics such as higher heart rate and reduced HRV in rest, irregular low/high-frequency spectral power density ratios, and lack of circadian variability are observed. These metrics are correlated with measures of physical and psychological function, but not measures of tenderness, possibly highlighting different etiological mechanisms (Staud, 2008).

Research has pointed out that the reduction in HRV in conjunction with other measures of dysautonomia,

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such as the inability to respond adequately to stressors, are predictors of poor cardiovascular health and prognosis, being associated with the development of coronary heart disease, myocardial infarction, ventricular and atrial arrhythmias, and sudden death (Su et al., 2015; Mansour et al., 2024). Furthermore, HRV dysfunction can also be a measure of emotionality in FM, which can reflect the inability of the brain to organize an appropriate affective response in the face of social demand and that can impact the manner in which the patient experiences pain. Interestingly, it was observed that artificially induced tachycardia induced an anxious behavior mediated by the posterior insula in an animal model (Hsueh et al., 2023). This observation stresses the existence of a bilateral interaction between the brain-heart interplay.

Therefore, HRV dysfunction in FMS may tell us different versions of two interconnected stories. The inability of the brain to keep the homeostatic state of the heart (and other prominent organs) – which is mediated by the humoral and immune systems, - and the role of the heart in generating altered neural feedback that may result in more nervous dysfunction in a pathological loop that can maintain the state of imbalance and disease, generating sleep disturbances and quality of life impairment (Al-shammary et al., 2023). Future research must clarify this intricate relationship, unveiling the specific mechanisms behind it and finding therapeutic targets to improve the treatment of FMS. Meanwhile, some of the potential mechanisms are highlighted by cumulative evidence.

Mechanisms for HRV dysfunction and the brain-heart interaction

Autonomic dysfunction is one of the main reasons for impaired HRV in FMS. It is suggested that decreased parasympathetic input occurs in response to chronic stressors, such as chronic disease. This creates a cascade of events from the overactivity of the sympathetic autonomic nervous system over the cardiac rhythms to long-term disordered nerve density. The brain perceives and controls blood pressure and cardiac function through the balance of the autonomic nervous system. Research has shown that cardiac anatomical and functional alterations are associated with brain abnormalities and risk of developing neurological diseases. The anatomical interfaces between brain and heart are starting to be disclosed as innovative technologies become available. From neuroimaging studies, the insula, cingulate cortex, frontal and prefrontal cortices, hippocampus, thalamus, striatum, and amygdala have shown the strongest correlations with HRV activity (Matusik et al., 2023). However crescent evidence points out to the periaqueductal gray (PAG), and the paraventricular nucleus of the hypothalamus (PVN), as the centers for autonomic control in the brain, in addition to the amygdala. PAG is mainly responsible for sympathetic control. It was observed that PAG deep brain stimulation decreased pain and increased HRV in chronic neuropathy, which highlights the role of sympathetic control in similar health conditions (Fujiu et al., 2023). On the other hand, the activity of the amygdala is an important neural marker of stress-related neurobiological activity and has a paramount role in the control of blood pressure and heart rate. Interestingly, a strong neural amygdala activity was observed in response to stress in females, which was associated with increased risk of coronary artery disease and poor cardiovascular outcomes (Yamanaka et al., 2018, Fujiu et al., 2023).

Inflammatory mechanisms are also involved in the HRV dysfunction observed in FMS and are related to the disrupted brain-heart interaction. Neurotrophins and inflammatory cytokines may play a role in the neural remodeling mentioned before. Nonetheless, the influence of the immune system on cardiac structure and function goes beyond that. Chronic inflammation may be present in the cardiovascular tissue in the presence of autonomic dysregulation, which highlights the role of the immune system as a potential mediator of brain-heart interaction to promote organ protection. The sympathetic autonomic nervous system presumably promotes the inflammatory response whereas the parasympathetic suppresses it (Fujiu and Manabe, 2022). That has strong implications for understanding the FMS clinical picture, in which dysautonomia and inflammation play a key role. Neuroinflammation is present in animal models of heart failure showing structural changes in microglia and astrocytes in the PVN, a neural center that plays a role on the stress response, and in the amygdala which the role was already mentioned. Interestingly, in those models the changes in PVN mediated by oxidative stress could be normalized by exercise training (Althammer et al., 2020; Koba et al., 2020). That highlights the potential role of physical exercise and other behavioral interventions in improving conditions in which the stress-response mediated by the brain-heart interaction is disrupted.

Small sensory and autonomic fiber neuropathy is a more recent discovery in FMS patients and reinforces both the dysautonomia and neuropathic features of this condition. Although the mechanisms behind the dysfunction of sensory ganglia in the dorsal root and in the autonomic ganglia are still under investigation, which include genetic causes, small fiber neuropathy is associated with aberrant neuroplasticity generated by trauma, infection, or genetic influences

(Martínez-Lavín, 2018). Nevertheless, these pathological processes seem to be mediated by the immune system as autoimmune markers are found in patients with widespread pain syndromes (Fujiu et al., 2022). Furthermore, postural orthostatic tachycardia is seen in young women with FMS, and it is also associated to small fiber neuropathy. Therefore, a potential causal link between a immune-mediated small fiber neuropathy in FMS patients could explain the multisystemic symptomatology present in this syndrome, including heart conduction conditions and increased risk of coronary disease in FMS patients (Tsai et al., 2015).

The dysautonomia and widespread inflammation play a relevant role in FMS and express the state of the interaction between the nervous system (the brain) and the cardiovascular system (the heart) as it is measured by metrics as the HRV. Using this interaction as a framework may help to better understand the neuropathic nature of FMS pathophysiology. Understanding these interactions can be used as part of therapeutic strategies. For instance, this brain-heart interaction could be used to optimize the neuromodulation protocols that target the fronto-vagal network, by selecting the best individualized montage by which a largest HR deceleration (parasympathetic engagement) can be achieved. These new approaches are called "Neuro-Cardiac-Guided" neuromodulation and ongoing studies are still testing the feasibility of this approach (Iseger et al., 2021). In this context, neuromodulatory strategies such as non-invasive brain stimulation may provide additional therapeutic benefits as this intervention seems to have a significant effect in reducing pain in FM (Caumo et al., 2024; Silva et al., 2017; Mendonca et al., 2016) and modulating the autonomic nervous system (Schestatsky et al., 2013), thus having a potential effect in two different pathways. Indeed, studies have been investigating the effects of pain control modulation and HRV changes (Rampazo et al., 2024, Legnon et al., 2023).

Finally, it can also help to develop potential therapeutic targets and strategies for the prevention of impairing symptoms, such as sensitized pain experience, exercise intolerance, inappropriate stress-response, emotional liability, and poor cardiovascular outcomes in this population.

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Conflicts of Interest

The authors declare no conflict of interest.

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