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LISBOA · PORTO

Hemispheric side and vagal nerve activity:

A systematic review

Dissertação apresentada à Universidade Católica Portuguesa para obtenção do grau de mestre em

Neuropsicologia

Por

Rodrigo Ribeiro Sandálio Dias Bento

Lisboa, 2021

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Sob a orientação de Drª. Rita Canaipa e Dr. Yori Gidron

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Theoretical Framework

Inflammation and Stress

Inflammation's main goal is to combat harmful infections or signal lesions to mobilize a response from the immune system. However after its resolution the inflammatory action must decrease to restore a physiologic and immunologic homeostatic balance in the affect area (Nathan & Ding, 2010; Serhan et al., 2007). Acute, time-limited and brief inflammation has benefits, especially during infections or injury (Ferreo-Miliani et al, 2007), but such benefit can be negated if exposure to pro-inflammatory agents last longer that it should. Evidence show inflammation is a key pathogenic mechanism for numerous diseases such as atherosclerosis, cancer and cardiovascular diseases (Coussens & Werb, 2002; Pearson et al. 2003). The persistent presence of certain pro-inflammation cytokines is an important factor for the development of chronic diseases. Cytokines such as IL-1, IL-6 and TNF-α are involved in the regulation of inflammation and are studied because of their dangerous properties that can advent from lengthen inflammatory action. Many studies are aimed to find antagonists agents to those cytokines to minimize their damage (Szlosarek & Balkwill, 2003; Voronov et al, 2003). The pharmaceutical industry had a lot of success in the development of anti-inflammatory medication but fails to meet the therapeutic needs for many cases of cancer, pulmonary disease, asthma, etc. since it operates separate from teams that work on these pathologies (Nathan & Ding, 2010). For an integrated therapeutic on nonresolving inflammation we need a more shared and collective understanding of its impact on various pathologies and its psycho-physiologic definition.

Unfortunately many factors in our daily routines can have an impact on our inflammatory response. One of the big agonist to inflammation's negative side (both chronic and acute) is stress. Considering it as an important variable related to inflammation, Connor & Leonard (1998) found that stress is associated with an increase of inflammatory cytokines and activation of the HPA -Axis. Stress inducing events can lead to an increase of pro-inflammatory cytokines such as IL-6 in plasma concentration measures. A probable cause is

the sympathetic response associated with increase adrenaline induced by a stressor. Animal studies, reported in Connor & Leonard (1998), observed in rats a stress sensation from within, as a result of immunological activation. These cases are a result of behavioral and neurochemical changes in the animals that end up inducing depression in the animal. In Maes et al. (1998), academic stress felt by students before an exam was related to an increase of pro-inflammatory cytokines and reduced anti-inflammatory response, especially in participants that were stress-prone. Steptoe et al. (2001) also studied, in an experimental design, participants after going through a short stressor and produced a higher level of pro-inflammatory cytokines and observed a significant increase in blood pressure. A temporal delay of 45 minutes in cardiac changes and a 2 hours delay in the levels of TNF-Alpha were also seen, when compared to baseline. In patients with depression, major life stressors present in their daily lives lead to an inflammatory response, and in turn change the patient behavior by enhancing depressive symptoms such as fatigue, sad mood, anhedonia and social withdrawal (Slavich & Irwin, 2014). Study of Connor & Leonard (1998) even concludes that the changes in the immune regulation that comes from stress (for its action on hypersecretion of cytokines) trigger the inducing depression. With other clinical samples, studies with stroke patients focus on minimizing the effect that inflammation was on the spread of the damage. A popular anti-inflammatory drug, Aspirin, was found to have a preventive effect of reducing the risk of stroke (Johnson et al, 1999). But if inflammatory cytokines are found in high concentration of plasma, stroke patients appear to have an earlier neurological deterioration than usual (Castellanos, et al. 2002). In Emsley et al, (2007), we find the conclusion that inflammation contribute in the pathophysiology of acute ischemic stroke, and we may add that stress for its prevalent influence on inflammation and arterial tension (Everson, et al. 2001) has a exacerbated function on those results. Study with rats also report a stress and inflammation correlation, LeMay, Vander & Kluger (1990) observed in their experiments that elevated psychological stress in mice lead to higher measure of the pro-inflammatory cytokine IL-6.

Overall effects of stress on inflammation are modulated by our sympathetic pathways. The sympathetic nervous system (SNS) is activated in a stressful situation, leading to an increase in blood pressure and heart-rate and a decrease in parasympathetic nervous system (PNS) activity. The stressful situation can be either cognitive or social, leading the same physiological activation (Muscatell & Eisenberger, 2012). The effect of stress therefore decreases our immune-to-brain system communication leading to the damage of inflammation we mentioned above. Since PNS is an important inhibitory pathway to inflammation's negative effects, the development of therapeutics that combats the stress factor and enhances parasympathetic activity is a point of major importance.

The importance of the vagus nerve

To counter such negative effects, the exogenous or endogenous factors that trigger the pro-inflammatory response also trigger an anti-inflammatory pathway. This anti-inflammatory response defends us from a prolonged homeostatic dysfunction through the HPA-Axis (Huston & Tracey, 201; Serhan et al., 2007). Responsible for the anti-inflammatory reflex is the vagus nerve. In fact the vagus is the major communicator between the brain and the immunologic system. It receives information from several visceral regions of our body. The same way it acts as an afferent pathway, it can also modulate an efferent response. In more detailed explanation, during an inflammatory response, activation of an afferent pathway is responsible for the communication between the immune system and the brain through the vagus, thus informing the brain of the location of the lesion and often initiating the presence of symptoms (fever, behavioral depression, decrease activity) to a probable pathogen. After the communication reached the brain, an efferent pathway of action can be activated, often termed as a cholinergic pathway. Such pathway functions as an inhibitory reaction to the inflammatory response to stop cytokine production (Tracey, 2009; Pavlov & Tracey, 2012). It occurs through depolarization of sensory neurofibers in the lesion area that leads information to the brain via the vagus (Ek et al., 1998). As a consequence, the

vagus also leads the efferent cholinergic signal to peripheral nerves (Borovikova et al., 2000; Tracey, 2007; Tracey, 2009). The descending anti-inflammatory response includes two pathways: Activation of hypothalamic pituitary adrenal axis - resulting with increased cortisol; and a systemic anti-inflammatory effect - the descending vagus reaches the celiac ganglion, where the cholinergic signal turns into an neuroepinephrine (adrenergic) signal, reaching specific T cells in the spleen. These splenic T cells then "represent" the vagus by secreting acetylcholine which binds to its receptor on residing macrophages, which then inhibits their production of pro-inflammatory cytokines (Rosas-Ballina et al., 2011). Different types of intervention aimed to improve our response to such maladaptive consequences of inflammation and consequently improve our recovery focus on the anti-inflammatory response. French et al. (2019) listed some of the most common models of anti-inflammatory mechanisms of treatments, including ketogenic diets and endocannabinoid therapy. One of the models delves on the stimulation of the vagus nerve. As mentioned above, the vagus nerve can lead to a better understanding of the inflammatory effects and our response to stressful events.

In various studies, the importance of the vagus was therapeutically shown when it acts as a main modulator in the beginning of headaches (Gaul et al., 2016) as well as in its role in recovery of cardiovascular and endocrine levels in subjects after a stressful event (Weber et al., 2010). Also in epilepsy, the vagal nerve has a main role as shown in many treatment studies (Gaul et al., 2016; Shahwan, Bailey, Maxiner & Harvey, 2007; George & Aston-James, 2010). After stimulation of the vagus, epileptic patients showed increase in blood flow in both right and left thalamus leading to a decrease in seizures the following weeks (Henry et al, 1999). Experimental cases with animals, through vagotomy or invasive vagus stimulation (Kuo, Lai, Huang & Yang, 2005; Ek, Kurosawa, Lundeberg & Ericsson, 1998) or non-invasive (Krahl, Senanayake, Pekary & Sattin, 2004) we can see the importance of the vagus to possibly treat various pathologies and that a low vagal tone may be a risk factor for chronic diseases (De Couck, Mrayec & Gidron, 2012; Gidron et al., 2018). A treatment for depression based on vagal stimulation was applied by Nahas et al. (2005)

on 59 patients with treatment-resistant major depressive episode. Long-term stimulation of the vagus showed long-term benefits to those patients in chronic or recurrent depressive episodes. Three major vagal stimulation non-invasive techniques are used in treating illness – vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Through these methods of stimulation we can obtain the benefits in increasing vagal tone, and are widely used in the treatment of epilepsy and headaches (George & Aston-Jones, 2010).

For neuropsychology the impact of the vagus is verifiable in many cognitive and behavioral domains. The vagus projects to the nucleus tractus solitarius (NTS) and activates cholinergic and noradrenergic pathways that are responsible for the release of acetylcholine. This neuromodulation serves a big propose in many behavioral and cognitive changes such as attention modulation and memory consolidation (Borland et al, 2018; Engineer et al. 2019). Such changes can be beneficial to neuronal plasticity and in the increase of long-term potentiating of synaptic efficiency, thus also fundamental for learning and memory (Korchounov & Ziemann, 2011). In Engineer et al (2019) a review of studies on stroke rehabilitation found that patients showed better behavioral results after pairing rehabilitation with vagal stimulation in promotion of cortical plasticity. Neuroplasticity is a main point in many neupsychological rehabilitation programs, especially in stroke patients, and the vagus can play an important role in development of a better prognosis (Husley et a, 2017). Considering the prevalence of the frontal lobe in the vagal communication, we find also that in various tasks that require inhibitory control, an enhanced vagus tone decreases errors resulting in a better performance of executive control, working memory and decision-making (Martin et al, 2004; Beste et al, 2016; Keute et al, 2018). This effect seems to derive from an influence of the vagus on the GABAergic modulation responsible for the cholinergic and noradrenergic pathways mentioned above. I can be viewed a potential pathway for treatment of attention disorders (Beste et al, 2016). Similar beneficial effects can be found in pathologies of neuropsychology's field of research and therapeutics. For cases of dementia, stimulation of the vagus is also seen as a potential

treatment in Alzheimer's disease and Mild Cognitive Impairment (MCI) (Keute, 2019). In Jacob et al (2015), a single session of vagus stimulation was effective in the enhancement of memory association in a geriatric sample. The overall impact of the vagus is still very much being researched but so far is showing that its implementation in neuropsychological rehabilitation may be a step to take in the future.

Heart-Rate Variability (HRV) and the vagus nerve

Heart rate variability (HRV) is a non-invasive index reflecting the activation of mostly the parasympathetic nerve system (Kuo et al., 2005). This index is used to understand the integrity of the autonomic nervous system as indexed by its impact on the cardiovascular system and its short-term effects as well as more long-term prediction of pathologies. As we established, many diseases occur due to chronic low-grade inflammation (Furman et al., 2019) and the vagal nerve informs the brain about inflammation (Ek et al, 1998) and then inhibits inflammation (Tracey, 2009). Using HRV enables the exploration of the vagal nervous reaction to inflammation, as reflected by cardiac control. (Liao et al, 1996; Tracey, 2007; Houston & Tracey, 2011). HRV is obtained by analysis of periodicities of beat-to-beat heart rate. These can be identified by spectral analysis and in function of time reach a frequency (Hz) value representative of HRV. Measuring hear-rate this way in junction with time data gives used the frequency of cycles that can be associated to parasympathetic or sympathetic activity (Liao et al, 1996). For example, a low level of HRV is associated with a higher risk for hypertension, coronary disease and acute cardiac events (Liao et al. 1996, Tsuji et al. 1996). In this case the low level HRV is synonymous for lower frequency cycles of HRV (LF-HRV) that will be explained in detail below.

HRV is established a potential risk factor for many diseases if is reported in low frequencies. Weber et al. (2010) observed that people with low HRV showed slower recovery to base levels on markers of blood pressure, cortisol and inflammation (TNF-alpha), after an acute stressor. Pro-inflammatory biomarkers such as the cytokines IL-1 and TNF-α appear to have a longer effect on the immunologic system in people with low HRV (Haensel et al. 2008,

Webber et, al. 2010). This prolonged inflammation can lead to a progression of atherosclerotic plaques resulting in heart attacks and strokes or other diseases like diabetes, sepsis and cancer (Huston & Tracey, 2011; Gidron, Kupper, Kwaijtaal, Winter & Denollet, 2007; Furman et al., 2019). Toledo & Junqueira (2009) found that in patients with Alzheimer's disease a higher cognitive deficit was negatively correlated with parasympathetic modulation. Also those participants observed with lower PNS had a statistical trend for higher sympathetic modulation, suggesting a influence on cognitive deficit and sympathovagal balance.

The recovery period after an inflammatory response ensures a return to physiologic and immunologic homeostatic balance in the affected area (Serhan et al., 2007). Still a deregulation of such processes may lead to a continuous inflammatory response, resulting in a chronic extension through time (Pavlov & Tracey, 2012). The anti-inflammatory reflex acts through the vagus in response, thus avoiding a lasting exposure to cytokines like IL-1 and TNF-alpha. (Huston & Tracey, 2011; Serhan et al., 2007).

High Frequency (HF) or Low Frequency (LF) are the two major points of the spectral analysis of HRV. HF-HRV values are associated with increased vagal activity and thereafter a parasympathetic response while a higher LF-HRV may either be reflective of sympathetic or parasympathetic response (Malliani, Pagani, Lombardi & Cerutti, 1991; Shaffer & Ginsberg, 2017). To consider these values an RR interval is obtained by HRV measuring that though evaluation of its variation can give us its frequency. The ratio LF/HF is found in the analysis of the RR variability rhythms that oscillate between both ends of the spectrum. Since it is misleading to completely separate vagal tone with sympathetic modulation of the heart, observation of the ratio of LF/HF can give us a detailed information on either inhibition or excitatory phase cycle we're measuring (Malliani et al, 1991; Chouchou et al. 2017).

A non-invasive method of stimulation (VNS, TMS, tDCS) can increase the activity of the vagus nerve (Frangos, Ellrich & Komisaruk, 2015) in order to produce an anti-inflammatory effect (Pavlov, 2008; Hoover, 2017). In

participants with high HRV frequency there's a corresponding high activity of the vagus nerve manifested by faster recovery from stress on multiple body systems (Weber et al., 2010; Huston & Tracey, 2011). On the other hand, the low frequency HRV subjects reveal a bigger preponderance of a sympathetic activation. In a study on the HRV activity of brain damaged subjects (Su et al., 2005), higher sympathetic activity was indicated by an increased LF-HRV accompanied with higher severity of the brain-stem damage. Also the severities of the damage lead to a decrease in HF-HRV. The decrease was hypothesized to be a consequence of damage in vagal center areas and mechanisms responsible for baroreflex sensitivity (which is a PNS related measure). Similar effects were found in Lampert et al. (2008) but on an inflammatory level with findings of a positive correlation between inflammation and coronary artery disease risk factors such as smoking, blood pressure, hypertension, etc. associated HRV. In Lampert's study, those risk factors were associated with decreased HRV. It is thus possible that increasing our HRV through vagal stimulation may lead to a healthier profile based on the studies reviewed here.

Hemisphere Lateralization

The modulation in our brain resulting from our immune system response to endogenous and exogenous factors can lead to functional alteration. A potential specification of our brain can be a product of such changes. Like speech in prevalent in areas of the left hemisphere for right handed people, or visual spatial memory in the right hemisphere are specializations in our brain that resulted from evolution. And on, the topic of cortical asymmetry, we find the study of Cerqueira, Almeida & Sousa (2008) focused on the importance of lateralization of the prefrontal cortex (PFC) in stressful situations and its response by means of activity of the HPA-Axis. The study found the left hemisphere much more vulnerable to the negative effects of stress leading to an impair regulation of the HPA-axis by the PFC left side. Furthermore, the stress response is lateralized in the brain with an enhancement of such response by the right hemisphere (Cerqueira et al., 2008; Lewis, Weekes & Wang, 2007). Lateralization is related with the immune system, since the right

hemisphere seems to be immunosuppressive while the left side immune-potentiating (Sumner et al. 2011) through parasympathetic activation. This can be found in Montenegro et al. (2011), in which left temporal anodal stimulation of the brain increased overall HRV and parasympathetic modulation with an also significant decrease of the sympathetic and sympatho-vagal balances. However, studies like Montenegro et al. (2011) either only contemplate the stimulation of one hemisphere or some do a bilateral stimulation but don't emphasize its effects on HRV (Bracco et al, 2017; Kaur et al., 2019) remaining unclear whether the right or left hemisphere mediate the functionality of the vagal nerve once compared with each other on a bilateral procedure. Also Henry et al (1999) in patients with epilepsy did left cervical stimulation of the vagus and found a bilateral cortical effect. Many studies can lead to similar results since it is common practice in VNS to stimulate the left cervical area (George et al. 2000). Focused on HPA-axis regulation, MacLullich et al. (2006) made comparisons between bilateral brain areas, finding that smaller left anterior cingulate cortex (ACC) was associated with higher dysregulation of the HPA-axis. This suggests a role in regulation on a cortical area by the ACC, and since dysregulation of the HPA-axis is found in conjunction with the ACC in depression and Alzheimer's disease it might have an immune preserving factor. The production of pro-inflammatory cytokines was higher in studies that observed that mice with higher left hemisphere activation, leading to a possible hypothesis that it's the right hemisphere that is responsible for the anti-inflammatory vagal effects (Neveu & Merlot, 2003) and that the HPA-axis and sympathetic innervations is responsible for immune regulation from brain (Kim, et al, 1999)

Considering differences in HRV frequency bands and lateralization there might be bigger importance on the left hemisphere to maintain a higher frequency of HRV while the right hemisphere seems responsible to enhance the sympathetic response characterized by low frequencies HRV. Vanneste, Fregni & Riddler (2013) study with patients with tinnitus and tinnitus related diseases they specify the importance of the insula in the brain and through HRV that LF-HRV increases and HF-HRV decreases if a decreased activity on the left

hemisphere insula is verified. Frisina, Kutlik & Barret (2013) did a retrospective study with data from a hospital's patients rehabilitation from head injury and infection. They observed a significantly higher number of patients with left side injuries ended with a variation of infection and it probably shows an immune deficit resulting from the damage on the left hemisphere. They verified a increase in the risk of poor immune function. Different behavioral changes deriving from the location of lesion is something very commonly expected. Robinson et al (1984) had reported a difference in symptoms depending on the side of brain lesion. Lesion on the left hemisphere leads to more severe depression than right hemisphere lesion patients. Its results are in accordance of the possibility that the left hemisphere is responsible for parasympathetic activity and that it may lead to prevention of depression but another factor was found, that an inappropriate cheerfulness was found in right lesion participants. If the left hemisphere is preserved in this case, how come the behavior exalted by the participants isn't inhibiting? It may that emotion and cognition have different aspect in the study of hemispheric lateralization than the communication the autonomous nervous system.

Sumner et al (2011) review found a dichotomy in the brain-immune communication with most studies revealing the left hemisphere as immunopotentiating. It was observed that at least one immune parameter in reviewed studies to worsen more in the left-than-right poorer function. In our review we will focus on an identifiable variable (HRV) to assess differences between hemispheres communication with the immunologic system.

Another validated measure for hemispheric lateralization (HL) is the line bisection test (Nash, McGregor & Inzlicht, 2010), which is a neuropsychological test. In this test, people need to mark on horizontal lines the middle of each line, whose distance to the real middle is then measured and averaged across 14 lines. In a recent study by Clement et al (2019), this test was used as a way to form 2 groups of participants in relation to their HL. They found a protective effect of the left hemisphere in coping strategies conjugated with their self-reported levels of daily stress and anxiety. Specifically, they found that emotion focused coping strategies were related to more daily stressors and

anxiety in people with right-HL, while problem focused coping strategies were related to less stressors and anxiety in those with left-HL. However, more research is needed on the associations between HL, vagal nerve activity and the immune response to stress, all performed in one study.

Hemispheric side and vagal nerve activity: A systematic review.

Abstract

The present systematic review explores the relationship between left versus right cortical activity or damage and vagal nerve activity. To better understand those pathways we identified various studies that presented results which tested hemispheric asymmetry and vagal nerve index of heart rate variability (HRV). Considering a probable lateralization difference in our brain-heart communication, we speculated that HRV would be associated with greater left hemisphere activity. We selected studies that measure HRV and either electrical brain stimulation, brain tissue concentration (voxel-based morphometry) and brain damage. We found a total of 9 studies that fits our criteria of selection. A positive mean effect size of 0.381 was found and evidences a medium effect of the left brain hemisphere on HRV parameters. Of the selected studies, 6 supports the conclusion that the left hemisphere is responsible for the increase in vagal tone and parasympathetic activity, 1 observed that it's the right hemisphere responsible for the same increase on vagus, and 2 studies consider the effect bilateral. In conclusion, our review presents evidence of a stronger role of the left hemisphere in vagal activity, using measures of HRV.

Lado Hemisférico e actividade do nervo vagal: Uma revisão sistemática

Resumo

A presente revisão sistemática explora a relação entre actividade, e dano cortical, entre hemisfério esquerdo versus direito e a actividade do nervo vago. Para melhor compreensão destas vias, identificámos vários estudos cujos resultados apresentam assimetria hemisférica testada e índices vagais como a variabilidade do ritmo cardíaco (HRV). Considerando a provável diferença de lateralidade na comunicação entre cérebro e coração, especulámos que o HRV esteja associado com maior actividade no hemisfério esquerdo. Seleccionámos estudos que mensuraram HRV em conjugação com estimulação cerebral, concentração de tecido cerebral (morfologia *voxel-based*) e dano cerebral. Um total de 9 estudos foi encontrado, passando os nossos critérios de selecção. Um efeito de magnitude positivo de 0.381 foi verificado na análise a estes estudos e evidencia o efeito médio por parte do hemisfério esquerdo em parâmetros de HRV. Dos estudos seleccionados, 6 suportam a conclusão de que o hemisfério esquerdo é responsável pelo aumento da tonalidade vagal e actividade parassimpática, 1 estudo observou que o hemisfério direito é o responsável pelo mesmo aumento no nervo vago, e 2 estudos consideram o efeito como bilateral. Em suma, a nossa revisão apresenta provas de um papel preponderante do hemisfério esquerdo na actividade vagal, usando medidas de HRV para o comprovar.

Introduction

During an inflammatory response, activation of an afferent vagal pathway is responsible for the communication between the immune system and the brain to mediate an efferent regulating response (Tracey, 2009; Pavlov & Tracey, 2012). The vagus has a major importance in promoting an anti-inflammatory response (Rosas-Ballina et al., 2011) thus being a focus of studies on the effects of pathologies that derive from inflammation (Huston & Tracey, 2011; Gidron, Kupper, Kwaijtaal, Winter & Denollet, 2007; Furman et al., 2019) and stress (Fink, 2010). This important pathway is relevant to headaches (Gaul et al., 2016), recovery from stress in cardiovascular, hormonal and immunological parameters (Weber et al., 2010), epilepsy (Gaul et al., 2016; Shahwan, Bailey, Maxiner & Harvey, 2007; George & Aston-James, 2010), to name a few examples. Many papers with animal samples revealed the same importance of the vagus (Ek, Kurosawa, Lundeberg & Ericsson, 1998; Krahl, Senanayake, Pekary & Sattin, 2004; Kuo, Lai, Huang & Yang, 2005;) and that a low vagal tone can be listed as a risk factor for chronic diseases (De Couck, Mrayec & Gidron, 2012; Gidron et al., 2018). Considering its wide importance, studies on therapeutics based on activating the vagus have emerged to reduce the negative side of inflammation and stress. Stimulation of the vagus can increase its modulation of inflammatory cytokines (Serhan et al., 2007; Huston & Tracey, 2011; Pavlov, 2008; Hoover, 2017; Frangos, Ellrich & Komisaruk, 2015;) and its overall contribution to the parasympathetic autonomous nervous system (Tracey, 2009; Montenegro et al., 2011). To measure this influence of the vagus, the index of heart-rate variability (HRV) has been used in many studies as a reliable index of parasympathetic vagal nerve activation (Kuo et al., 2005).

Use of HRV enables the exploration of the vagal nervous' reaction to inflammation, as reflected by cardiac control (Liao et al, 1996; Tracey, 2007; Houston & Tracey, 2011). A low level HRV is associated with higher risk of coronary disease and acute cardiac events (Liao et al. 1996, Tsuji et al. 1996) and a higher exposure to inflammation and worsens recovery from it (Haensel et al. 2008). Therefore the hypothesis of counterbalancing such negative effects by increasing HRV was proposed by the above mentioned research on the

therapeutics focused on the vagus. Data obtained from HRV measurements were associated with either parasympathetic or sympathetic nervous regulation. Through HRV spectral analysis of frequency, we can find two main measures of either High Frequency (HF) or Low Frequency (LF). HF values are associated with increased vagal activity and therefor a parasympathetic response, while a higher LF may signal a higher parasympathetic and sympathetic response (Malliani, Pagani, Lombardi & Cerutti, 1991; Shaffer & Ginsberg, 2017). A ratio between HF/LF is also of mention since it helps to differentiate between a sympathetic and a parasympathetic response (Chouchou et al. 2017). Other variables of importance such as SDNN (standard deviation of the normal-to-normal interval), BRS (baroreflex sensitivity), RSA (respiratory sinus arrhythmia), RMSSD (route mean square of successive NN differences) and pNN50 are often obtained as time domain measure of HRV analysis as a measure associated with enhanced parasympathetic activity (Task Force of the European Society of Cardiology…, 1996; Bernston et al. 1997; Rovere, Pinna, Raczak, 2008). On the other hand variables such as SCL (skin conductance level) and HR (heart-rate) are used as measures of the sympathetic autonomous nervous system (Chrichley, 2002).

A question that remains in discussion is whether one or both hemispheres regulate the autonomous nervous system and each of its branches, namely the sympathetic versus parasympathetic responses. During stress an enhancement of activity of the right hemisphere has been observed (Cerqueira et al., 2008; Lewis et al., 2007). Furthermore, while the right hemisphere has immunosuppressive effects, the left hemisphere seems to be immune-potentiating (Sumner et al. 2009, Vanneste & Riddler, 2013) possibly through less sympathetic and more parasympathetic activation. However in studies such as by Neveu & Merlot (2003), the production of pro-inflammatory cytokines was higher in mice with higher left hemisphere activation leading to a possible hypothesis that it's the right hemisphere that is responsible for the anti-inflammatory vagal effects. Since some studies either only examine the stimulation of one hemisphere (Montenegro et al., 2011) while others perform bilateral stimulation but don't emphasize its effects on HRV (Bracco, Turriziani, Smirni, Mangano & Oliveri, 2017; Kaur et al., 2019) it remains unclear whether

the right or left hemisphere mediate the functionality of the vagal nerve once compared with each other in a bilateral procedure.

The purpose of the present review is to examine which hemisphere seems to be responsible for the vagus activation and resulting parasympathetic effect. Thus, this study will focus on reviewing studies whose procedure considers both hemispheres either by stimulating both or by examining effects of damage in each hemisphere, and including a measure of HRV. Reviewed studies may also present an experimental or quasi-experimental design and stressful events in its methods as a way to trigger a regulatory nervous response. In our research we found initially more evidence of mediation of HRV by the left hemisphere and we thus hypothesize that our review will support this conclusion.

Method

Literature Search and selection criteria

As a way to find the published papers discussed in this review, we used an online computer based search in scientific databases such as Pubmed, PNAS, Science Direct, Springer Link, Researchgate and Wiley Interscience. In our search we focused on the following keywords: “HRV”, “lateralization”, “lateralization”, “vagus”, “vagal”, “asymmetry”, “cortical” and “cerebral” using more than one combination with these keywords. Once studies were found with these keywords and written in English, after reading the title of the study we filtered its pertinence for our review by reading its abstract and its method (fig.1). If in an article included a cortical bilateral procedure of measure or intervention and a measure of HRV, the article would be approved for the review. It was not necessary for the paper to target the question of asymmetry of the vagus or of the HRV measures as a study hypothesis as long as they had the necessary values measured and a procedure that would lead to a plausible conclusion of difference between hemispheres (although most studies considered the lateralization in either the discussion or as a potential finding in the introduction). The studies had to be experimental (with human subjects, healthy or not, regardless of gender and age) and published between 2010 and

2019. Only articles for which we had full access to were considered. In some cases, we used studies references to indentify additional studies

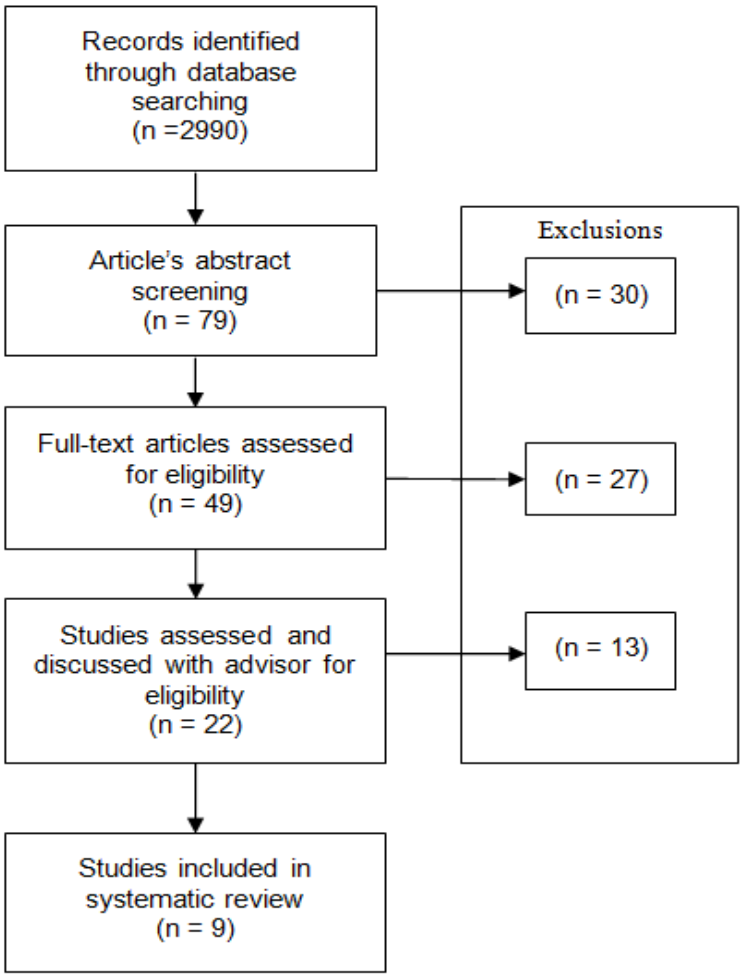

Fig. 1 Flowchart representative of the research and selection made. Once selected studies relevant to our review, a exclusion criteria was applied to reach the final 9 studies analyzed in this review

Extracted information

A table of contents of the resulting selected articles for the review included the authors and years sample of participants, its variables and measures, intervention and results. Regarding its results, our review focused on statistically significant results, although in some cases, we refer to other pertinent results. Then, the effect size calculation was made for every study, and finally across studies, as explained below.

Effect size assessment

Of the selected studies, HRV measures (e.g. HF-HRV, RMSSD, etc.) were used for calculation of effect size (Cohen's *d*= $(M_2-M_1)/SD_{pooled}$) if such parameters were clearly described in the article. If other measures of importance were found, the same was applied if it was relevance to identify the power of differences between hemispheres in relation to vagal tone. For example, we examined differences in HRV between patients with left versus right strokes, or between stimulating the right versus left hemisphere.

Quality scores

For quality assessment of the selected studies we used the STROBE scale statement (Von Elm, et al. 2007). -The scale consists of 22 (yielding a total score of 32) that guide our evaluation of the studies' quality from its title & abstract, introduction, methods, results, discussion and other information given. This assessment was used to evaluate the scientific methodology of the selected articles and their presentation.

Results

Selected studies

A total of 9 studies were selected for review after the application of our selection criteria (Table of Contents *in Appendix*). The studies were published from in-between 2013 and 2018. Five of those studies had experimental methodology and four were quasi-experimental. In addition, five studies used only healthy participants and four studies used participants with clinical conditions.

Quality Assessment

After applying the 22 item STROBE cheklist, a mean of 63.5% (SD=8.72) of items checked was obtain among the nine reviewed articles. Gulli et al. (2013) had the lowest percentage of items with 46.8% (15/32) and Sturm et al. (2018) the highest with 78.1% (25/32). Comparing the absolute score of selected articles with the mean results from Adams, Benner, Riggs & Chescheir (2018) where an evaluation on the quality of accepted articles on obstetrics was reported (M=23.2; SD=2.7), of the reviewed studies 4 had an absolute score equal or higher, 4 were a standard deviation below and one study had a significantly lesser score.

Effect size

The effect size calculation was made to reviewed studies that provided the necessary data to do it (table 1). The intention was to define a mean effect size between studies. The effect size were to be interpret using Cohen's criteria (1988) in which a small effect size is represented by $r>0.1$, medium effect size a $r>0.3$ and a large effect size a $r>0.5$. Considering this, one study revealed a small mean effect (0.089) and two had a medium effect and other two a large effect size. The remaining studies had either insufficient or no presented data needed for mean effect size calculation. The mean effect size of all effects from eligible studies was 0.381. This medium effect size reflects the lateralization and HRV parameters relationship. A positive correlation means the effect is explained by a leftward activity and negative one by rightward activity. Of important parameters, HF-HRV presented a mean size effect of 0.924 and LF-

HRV a mean size effect of -0.634. Overall of effects that use more valid PNS parameters (HRV, HF-HRV, CVI, SDNN, pNN50 and RMSSD) had a mean effect size of 0.706.

Table 1. Mean effect size

Article	Effect	Effect size (*r*)	Mean ES
Brunoni et al. (2003)	HF-HRV left vs right cathodal stimulation LF-HRV left vs right cathodal stimulation	d= 0.084 d= 0.095	0.089
Gulli et al. (2013)	LF-RR left vs right stimulation HF-RR left vs right stimulation LFnu left vs right stimulation HFnu left vs right stimulation	d= 0.496 d= 0.586 d= 0.556 d= 0.835	0.618
Tegeler et al.	HF-HRV left vs right stimulation (≥5% Asymmetry) HF-HRV left vs right stimulation (≥10% Asymmetry) HF-HRV left vs right stimulation (≥20% Asymmetry) HF-HRV left vs right stimulation (≥30% Asymmetry) HF-HRV left vs right stimulation (≥40% Asymmetry) HF-HRV left vs right stimulation (≥50% Asymmetry)	n/a n/a n/a n/a n/a n/a	
Guo et al.	Left worse than right atrophy and lower basal CVI Left side atrophy predictor of CVI Left ACC x HRV Left Insula x HRV Left Postcentral x HRV Right ACC x HRV Right IFG x HRV ACC - Left Insula connectivity x vagal tone	d= 1.001 d= -0.324 n/a n/a n/a n/a n/a n/a	0.343
Dziembowska et al.	Left vs right (log alpha power) pair 1 Left vs right (log alpha power) pair 2 Left vs right (log alpha power) pair 3	n/a	
Brugnera et al.	Right Channel NIRS x HR control (stress) Right vs left channel (baseline) Right vs left channel (condition – stress)	0.529 n/a n/a	0.529
Constantinescu et al. (2018)	Resting: SDNN left vs right stroke RMSSD left vs right stroke pNN50 left vs right stroke LFnu left vs right stroke HFnu left vs right stroke Deep breathing: SDNN left vs right stroke	 0.545 0.916 0.895 -2.445 2.398 0.361	

	RMSSD left vs right stroke pNN50 left vs right stroke LFnu left vs right stroke HFnu left vs right stroke Standing test: SDNN left vs right stroke RMSSD left vs right stroke pNN50 left vs right stroke LFnu left vs right stroke HFnu left vs right stroke	1.268 0.622 -2.108 1.248 0.408 0.469 0.309 -0.4 0.391	0.325
Sturm et al. (2018)	Low RSA and Atrophy on : - Left vIA - Left Inferior temporal lobe - Left vIA - Left ACC connectivity - Left vIA – Right ACC connectivity - Right vIA – Right ACC connectivity	 d≥0.2 d≥0.2 n/a n/a	
Wei et al. (2018)	GM volume and HF-HRV - Right putamen - Right caudate - Right amygdala - Right Insula - Right sTG - Right tempral pole - Right parahippocampal gyrus	 n/a	

LFnu and HFnu = normalized units (spectral analysis) ; CVI =cardiac vagal index ; ACC = anterior cingulate cortex; vAI = ventral anterior insula; NIRS = near infrared spectroscopy; GM = grey matter; sTG =superior temporal gyrus

Experimental and Quasi-Experimental Studies

Brunoni (2013)

The study of Brunoni et al. (2013) hypothesized that, comparing to a control group, the stimulation of the left cortical area of the dorsolateral prefrontal cortex (DLPFC) through transcranial direct current stimulation (tDCS) would lead to a higher decrease of sympathetic and HPA activity than a right cortical stimulation. They included 20 healthy participants through 3 randomized groups: sham-stimulation, left anodal and left cathodal stimulation (the anodal stimulation on the left means increasing its excitability and a right cathodal on the other side has an opposite effect). Participants were also shown pictures with neutral, positive or negative valences during stimulation. The researchers found that a single stimulation of the DLPFC changed the HRV and cortisol according to its polarity and valence of images presented. When presented with negative images the left anodal group had lower levels of salivary cortisol and

higher HF-HRV values compared to the control group (sham-stimulation). Comparing with the left cathodal group, the left anodal group had also lower levels of cortisol in the saliva. This study verified therefore a parasympathetic gain thanks to the influence of the electric stimulation of the tDCS on the left DLPFC, although only significant during a negative valence event. It was discussed that it might be because the setup of negative imagery demands a specific and greater processing of the DLPFC or reflects a stressor during which the effects of vagal regulation may be more manifested.

Gulli et al. (2013)

Gulli et al. (2013) designed an experimental procedure with repetitive transcranial magnetic stimulation (rTMS) on both hemispheres. Low frequency rTMS is responsible for inhibition of cortical firing, while high frequency rTMS is thought to activate it (Cusin & Dougherty, 2012). It was aimed that a low-frequency stimulation of the prefrontal lobes would lead to changes in heart rate, blood pressure and total peripheral resistance. The study used 12 healthy participants that would be stimulated on one side (5 subjects started on the dominate side,7 on the non-dominate) of the prefrontal lobe for 8 minutes with rTMS of 0.7Hz of frequency. This was followed by a resting phase, then by a second stimulation on opposite side and finally by another resting phase. Their statistical analysis revealed success in the rTMS since changes in cardiac parameters were found during the stimulation period that would later terminate in the resting phases. Comparing with baseline, participants after stimulation showed signs of bradycardia but only the results of the right hemisphere rTMS showed significant results. Also after right rTMS, a significant increase was found in total power of HF-HRV and the LF/HF ratio shift towards HF-HRV dominance which could be explained by a decrease of sympathetic activity or by an increase of the vagal tone, or both.

Tegeler et al. (2015)

The main aim of the study was that a high asymmetry recording may be a reflex of autonomic regulation from both hemispheres depending on dominance, with left dominance being indicative of parasympathetic activation and right dominance reflective of sympathetic activation. With a sample of 131 participants with diverse clinical conditions, Tegeler et al. measured the heart rate, HRV (spectral HF- HRV) and baroreflex sensitivity (PNS measure). 30 min after the recording session, participants underwent a brain electrical assessment using a standard HIRREM technique with a two channel scalp in each temporal hemisphere, for at least six different locations. The study reveals that participants with rightwards dominance manifested a higher resting heart rate and lower BRS. Although it was found a tendency for leftwards dominance participants to have higher HRV values in time and frequency domains of HRV, these results were not significant. The study in the end supports a correspondence between temporal electric asymmetry measurements and autonomic regulation of cardiac function in both a possible afferent and efferent pathway.

Dziembowska et al. (2015)

For their study, Dziembowska et al.(2015) used HRV biofeedback (HRV-BFB) as a method of intervention their experimental design. They hypothesized that biofeedback training would lead to changes in the autonomic and central nervous system and in the participants' anxiety and self-esteem. The study was conducted on 41 male athletes. The participants were randomized into two groups (biofeedback and control). Measures of HRV and EEG were obtained before after biofeedback sessions, 21 days after. The results of the study revealed significant changes in three out of four HRV parameters compared to baseline. The EEG verified alpha asymmetry in three pairs of electrodes of which the biofeedback group exhibited right frontal asymmetry and greater frontal alpha activity, reflecting right activity in these regions. Also in the biofeedback group a shift towards left parietal and left occipital areas of alpha asymmetry was found after training. In comparison no differences were

significant in the control group in both HRV and EEG recordings. Also in terms of the self-report questionnaires only the biofeedback group showed a significant decrease in state anxiety levels and stress. These results reveal that HRV-BFB can cause lateralization in brain activity, with the dominant side different according to the precise regions examined.

Guo et al. (2016)

In this study, the exploration of lateralization in the autonomic regulation was made by including 17 subjects with bvFTD (behavioral-variant of frontotemporal demential) and a control group of 19 participants. The study tried to explain how the diminished cardiac vagal tone can be traced back to a perturbed hemisphere due to bvFTD. ECG was used to measure HRV parameters. A voxel-wise degree of centrality permitted statistical tests for correlation between right or left hemisphere voxels and a cardiac vagal index (CVI). Patients with bvFTD had significantly lower levels of parasympathetic tone as indexed by CVI, HRV and RSA, compared with to the healthy group. To corroborate those results, a higher resting heart rate in bvFTD was found. fMRI with a continuous HRV index recording was made. In healthy participants, such a procedure revealed a linear correlation between HRV and activity of predominantly left hemisphere regions. Yet, if the threshold for the BOLD signal was minimized, a correlation with some areas of the right hemisphere with HRV was also found. In terms of salience networks, connectivity in both hemispheres was found related to pre-established CVI, but in the case of the right hemisphere, it was because of interactions of the right frontal insular area with left structures of the brain. A left side ipsilateral connetivity (frontoinsular network with anterior cingulate cortices, temporal lobe, occipital lobe and ventral putamen) is a strong predictor of CVI**.** A voxel-wise comparison was made between hemispheres and only a significant lateralization was found on the left anterior insula. Finally the study also used the cerebral atrophy of the bvFTD as a correlate of diminished cardiac vagal tone. A worse left-than-right bvFTD atrophy was found to be related to worse cardiac vagal tone (especially in pregenual anterior cingulated cortex and the fronto-insula)

Constantinescu et al (2017)

Constantinescu et al. gathered 15 participants with left side ischemic stroke and 15 with right side ischemic stroke and compared their resting and stimulated HRV parameters to those of a healthy control group. The initial phase was a resting position. After that the participants had to do a deep breathing test to assess a parasympathetic response and a standing test (from supine to orthostatic position). From this procedure the results revealed that left hemisphere stroke participants had higher parasympathetic control evidenced by RMSSD, pNN50 and HF-HRV values in resting state compared with right stroke participants. Also during rest, right side stroke group found a higher correlation with sympathetic control. During deep breathing, a pronounced vagal influence (RMSSD and HF-HRV increase) was found on participants with left side stroke. Finally, in the standing test a decrease parasympathetic control was found in the right stroke group compared to control. The study's conclusion indicates that their results are in concordance with the left hemisphere role in cardiac control by bradycardia and increase in HRV. The right hemisphere stroke group has a more pronounced sympathetic control.

Brugnera (2017)

In Brugnera et al. (2017) there was the development of a stress inducing procedure accompanied by reports of anxiety and depression, a cortical 2-channel near-infrared spectroscopy (NIRS) on the prefrontal lobe and a portable ECG. The researchers hypothesized decrease of parasympathetic activity and increased heart rate during the experimental trial, hypothesized increase of the right prefrontal cortex from the stressful event and a possible positive correlation between the frontal lobe and the autonomic nervous system. A sample of 65 healthy students participated. Two randomized group were formed, one assigned to do a simple math task (control) and the other a stress inducing math task (experimental). ECG and NIRS measures were obtained during a resting and stressful (condition) phase. Correlations between NIRS measurements and heart rate validated the involvement of right frontal areas in the sympathetic response to the stressful task (analysis on cortical

interrelationship found a correlation between heart-rate and right-side activity during both resting and stressful conditions). In its conclusion Brugnera et al. (2017) considered that the lateralization was apparent once correlations were made between such signal values and heart rate and if considering correct answers in the math task (leftward PFC activity participants had betters results). But in the end HRV parameters showed no difference between hemispheres. Tough not supporting a role of one of the hemisphere in regulation HRV, this study does show relations between HR, a sympathetic index, and right frontal activity.

Sturm et al. (2018)

The study done Sturm et al (2018) proposed an experimental setup to test network patterns related to the parasympathetic and sympathetic nervous systems. A sample of 47 participants was divided into two groups, where one was composed of 23 patients with bvFTD and the other with 24 healthy subjects. A first step of the procedure was made for recording of baseline levels of autonomic physiology while viewing various short films as a resting phase evaluation. Participants underwent structural and functional imaging and a further analysis was made to highlight the key network edges and areas associated with the RSA and SCL values. Results revealed an important association of the ventral anterior insula and anterior cingulate cortex connectivity with the PNS activity(a lower volume of the ventral anterior insula can lead to similar results). This was found in bvFTD participants in whom their lower RSA was related to the atrophy of the left insula and other regions. Weak functional connectivity between left hemisphere structures and/or right hemisphere structures (both inter-hemisphere connections and intra-hemisphere) was related to deterioration of the parasympathic vagal tone. In the case of a strong connectivity between the bilateral anterior cingulate cortex and right hemisphere amygdala/hypothalamus the RSA was significantly lower. These findings suggest that not only the integrity of the left anterior insula connections modulates the parasympathetic function but a suppression of the anterior cingulated cortex connectivity with the amygdala and hypothalamus (especially of the right hemisphere) is necessary to preserve the vagal tone.

Wei et al. (2018)

With the voxel-based analysis the study of Wei et al. (2018) looked into a sample of 185 healthy participants to associate its brain morphometry with vagal control, an considered gender and age. The hypothesis presented was that gray matter volumes in certain brain regions correlate with the HRV and cardiac function. Structural fMRI voxel model was obtained and covariated with HF-HRV in their statistical approach. In their results, Wei et al (2018) found a negative correlation between gray matter volume of the right areas and HF-HRV. A similar correlation was found in the bilateral striatal and limbic structures. No positive correlation was found with areas of both hemispheres and HF-HRV and no correlations were found with LF- HRV. Concerning heart-rate, the study found a negative correlation with the right side cerebellum. In their discussion Wei et al. (2018) mentioned the problem of defining which hemisphere is responsible for parasympathetic control and concluded that their findings of a bilateral correlation of the striatal and limbic regions may suggest that both hemispheres are responsible and that there's a significant suppressive effect on HF-HRV associated with the right hemisphere.

Discussion

In this systematic review a total of nine published papers were summarized and studied in order to reach a conclusion on hemispheric lateralization and vagal tone. Of the nine studies selected, six of them (66.7%) either conclude or show evidence that it's the left hemisphere responsible for increase in vagal tone and consequently activation of the PNS (Brunoni et al. 2013, Tegeler et al. 2015, Guo et al. 2016, Dziembowska et al. 2016, Sturm et al, 2018, Constantinescu et al. 2018). One study (11.1%) supported the hypothesis that the right hemisphere is responsible for PNS activation (Gulli et al. 2013) and the remaining two studies (22.2%) considered a bilateral effort (Brugnera et al. 2017 and Wei et al. 2018). Although the reviewed studies were heterogeneous between them in participants, methodology, instruments, etc., a unanimous effect could be found that points to an importance in hemispheric

lateralization in our brain communication with the nervous system. Our calculations of mean effect size for the reviewed studies presented correlations (mean=0.381) support our assumption that the left hemisphere is responsible for vagal tone reflected in HRV parameters. In our calculations, we found the same evidence when calculating the effect size of values for HRV parameters valid for measure of PNS activity and vagal tone. The quality assessment of the reviewed studies showed that four of the studies were of expected normal quality, four slightly below and one had much lesser score. Our review presents a small sample with a verifiable majority of studies that report results in favor of the hypothesis that a difference is found between hemispheres, in which the left hemisphere appears to potentiate the vagal tone, increase HRV and, as conclusion, the PNS. This point presented as our study's purpose for investigation was met in this systematic review. Therefore, it is possible that the SNS activity is potentiated by the right hemisphere (immunosupressing effect) but since a limitation of our review was its higher focus on HRV parameters that reflect PNS activity we present a conclusion with higher certainty on the left hemisphere's role.

Through our aimed review on HRV parameters we found convergence with other studies that used different parameters that reflect PNS or SNS activity. Benarroch (1993) reported that a leftward activity (particularly on the left insula) may be a dominant response for bradycardia and depressor effects, while a rightward activity seems responsible for tachycardia and pressor responses. The same effects can be reveled through HRV parameters such as the ones in our reviewed studies. Other studies verified that left hemispheric activity leads to an immune-potentiating signal increase (Kang et al. 1991; Gruzelier et al. 1998) which highlights the role of the vagus as an efferent pathway. This role can be corroborated by the increase of HRV and vagal tone by left hemisphere stimulation in other studies (Wittling et al. 1998; Montenegro et al. 2017). In studies that used stressors to test hemispheric lateralization, we find a seemingly consensus that the right hemisphere is responsible for the activation of the HPA-axis and inflammatory response to stress (Cerqueira et al. 2008). As a counterbalance to this effect, the left hemisphere plays an inhibitory

role on the right hemisphere action (Sullivan 2004; Bracco et al. 2017), thus acting also as a modulator of the stress response. These finding are in concordance with our results since the vagus is a major modulator of anti-inflammatory response to stressful events (Ohira et al. 2013, Weber 2010; Brenner et al. 2020).

To better explain the vagus mechanism in the increase of certain HRV parameters and parasympathetic communication we can look at immune response. Left side frontal activity is found to have positive correlation with absolute lymphocyte count, cytotoxic/suppressor cells (CD3+8+) and anti-inflammatory cytokine such as IL- 1β, IL-6 and TNF-α (Borovikova et al. 2000; Stoyanov et al. 2012) and vagal tone stimulation can be used for inhibition of referred pro-inflammatory agents (Tracey, 2009; Rosas-Ballina et al, 2011; Pavlov & Tracey, 2012).Since HRV is a measure for vagal tone, decreased HRV is associated with lower recovery from inflammation, reflective of a impaired PNS cholinergic response (Weber et al, 2010;Lampert et al, 2008; Williams et al. 2019). Considering that these effects depend on lateralization (Neveu, 2008; Neveu & Merlot, 2003) our review finds that the left hemisphere is responsible for parasympathetic response via the vagus and it can be verified in HRV. Studies with participants with brain lesion like Ivashkova et al. (2002) revealed a decrease in anti-inflammatory cytokines due left hemisphere stroke. Other articles such as Kirchner et al. (2015) and Ghchime et al. (2016) used patients with temporal epileptic support our conclusion of lateralization and of parasympathetic activity modulated by left hemisphere and sympathetic by the right hemisphere.

Our study can have a clinical impact on localization of treatment. In epilepsy, vagus nerve stimulation is often use as a method of treatment and is used on the left vagal side (Schachter & Saper, 1998). Considering our analysis on hemispheric asymmetry, cortical stimulation can lead to similar results if the desired effect involves enhancing the parasympathetic response and HRV. In the treatment of patients with depression, higher activity of the left frontal love seems to be associated with positive emotions. Using RSA as an indicator Oveis et al. (2009) study found that this association can help in depression

therapeutics. Also Newell (2005) found that increase in HF-HRV, as well as left brain lateralization, was positively correlated with positive emotions. Lee, et al (2014) created a bihemispheric model for cases of traumatic stress and verified that rightwards dominance was associated with high arousal trauma, while leftwards dominance with freeze tendencies, illustrating also the sympathetic and parasympathetic asymmetries discussed. The importance of recovery from various pathologies to a homeostatic balance can be achieved through vagal intervention and increasing HRV values (Weber et al. 2010). In some cases this recovery is a response to sympathetic reactivity (Steptoe et al.2001) that can be modulated by the vagus.

Critiquing the review studies' methodology, Dziembowska et al, (2015) after biofeedback training found differences between hemispheres using changes in EEG alpha power. This measurement seems to indirect to find asymmetric influences caused by the biofeedback training, and stronger correlation between the EEG values obtained and HRV differences could be explored to validate the assessed laterality. The same critique can be made to Brugnera et al. (2017) since it used NIRS that measured changes in oxy-haemoglobin. It can detect difference in hemispheric activity but the math task can lead to confounding effects in their conclusion. Both studies lack precision in their laterality assessments. In Gulli et al. (2013), rTMS stimulation was made at a frequency 0.7Hz. A calibrating frequency to each participant, considering its small sample, to ensure that the stimulation is efficient would negate probable confound effects. Comparing it with Gross et al. (2007) meta-analysis on rTMS use in patients with depression, a low frequency magnetic stimulation started at 1Hz. Without a proper explanation for the value of their rTMS, Gulli et al (2013) article seems incomplete in that regard. Constantinescu et al (2017) at first seems to indicate that the vagal tone is influenced by the right hemisphere since it deals with stroke patients. In their article, left stroke patients had higher HRV values, but since the lesion is on th left hemisphere it can lead to the conclusion that such HRV values are a consequence of a preserved right hemisphere. If it wasn't for its discussion, defending that their results reflect a positive role of the left hemisphere on parasympathetic response, it would

induce us into thinking the non-lesion hemisphere was responsible for the results obtained in HRV. It seems although that it is a common occurrence in stroke related studies and HRV. A better explanation of their rationale would clarify the non-intuitive correlation between high values of HRV and stroke areas. A critique on the presentation of results can also be made to some studies. A lack of standard deviation or correlation values limited calculations on effect size of many studies. Wei et al. (2018) presented in their results only correlations between right structures of the brain although they were made for both hemispheres.

Studies Limitations and future directions

In sequence with a critique on the presented results, we limited our review by not seeking data from the authors of the studies selected. Also, the selected studies presented various HRV parameters that we highlighted as parasympathetic measures, but some were transformed in statistical analysis or obtained in various ways. These heterogeneous parameters may be measures of HRV or PNS but a more focused review on some of them would result in a more grounded conclusion. Unfortunately that would also limit the amount of eligible studies since not all present their results using the same variables of interest. Another limitation is found in our research which is only apparent at the end of our analysis. After our systemic review, the insight and knowledge obtained from this study could have been useful for a more refined and precise research. There's a probable limitation that other articles with useful methodology to our question of study were not included. In that regard we only can gain from this experience and learn to do better in the future. In that future we hope our study can help to direct vagal therapeutic to the left side of our brain. That the treatment of patients with brain lesion can encapsulate the location of impairment and our conclusion on hemispheric lateralization, and that the inflammatory damage can be minimized by stimulation of the vagus nerve and preservation of the autonomic regulation that derives from our left hemisphere.

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Appendix -1

Table of Contents

	Sample	Lateralization	HRV and other meaningful measures	Design	Results	Quality scorre
Brunoni et al. (2013) Left	20 healthy (mean age of 24.9; SD=3.8)	Transcranical direct current stimulation (tDCS) -Cathodal -Anodal -Sham	LF-HRV HF-HRV	Experimental	HRV – interaction polarity x valence found – in post hoc, differences found for left anodal vs sham stimulation. The effect was specific for HF-HRV Cortisol – significant differences for the left anodal stimulation vs sham. Main effect for polarity found with low values on anodal and higher on cathodal stimulation (both left). Polarity effects are also specific for valence. HRV x Cortisol – inversely related after anodal stimulation (HF-HRV)	21
Gulli et al. (2013) Right	12 healthy (mean age of 35; SD=2.3)	Repetitive transcranial magnetic stimulation (rTMS)	LF-HRV HR-HRV LFnu HFnu SP (systolic pressure) DP (diastolic pressure) RR LF-SP Cortisol	Experimental	rTMS induced bradycardia after right hemisphere (prefrontal lobe) stimulation Also right rTMS induces an increase in the HF measures in normalized units (33.4 ± 6.9 vs 44.6 ± 7.4; p = 0.048) and shift of the LF/HF ratio towards HF predominance (3.8 ± 2.1 vs 1.6 ± 0.6; p = 0.042)	15

Tegeler et al. (2015) Left	131 participants (mean age of 43.1) with diverse clinical conditions and depressive and insomniac symptoms	HIRREM approach EEG	HF-HRV Standard deviation of normal-to-normal interval (SDNN) Heart-Rate Blood Pressure Baroreflex sensitivity (BRS)	Quasi-Experimental	Right hemisphere dominance was found on subjects with 5% to 30% asymmetry associated with higher resting heart rate Subjects with 40% or greater and 50% or greater asymmetry, rightwards dominance was associated with lower BRS All participants on a asymmetry cutpoint showed a leftward dominace associated with higher HRV and in HF spectral domain (not significant differences compared to rightward dominance)	21
Guo et al. (2016) left	17 participants with bvFTD and 19 healthy participants (control)	Structural and Functional MRI -seed-based ROI analysis -Brain voxel-based model mapping	Logarithm of HRV (logHRV) Cardiac Vagal Index (CVI) Respiratory Sinus Arrhyhmia (RSA) Skin Conductance Level (SCL) Cardiac Sympathetic index (CSI) NEO-PI-3 NPI on first-degree relatives Boston Naming test Peabody Vocabulary Test Semantic and Phonetic word generation Digit-span Cardiac Vagal tone: ECG Pulse oxymetry (PhLEM	Quasi-Experimental	Cardiac vagal tone was lower in bvFTD experimental group. Diminished cardiac vagal tone associated with reduced left-predominant salience network intrinsic connectivity and structural integrity Coupled HRV results with predominantly left structures (frontoinsula and anterior cingulated cortices and anterior insula)	20

			toolbox)			
Dziembowska et al. (2016) left	41 Healthy athletes (age 16 to 21, mean 18.34; SD=1.36)	EEG -Alpha and theta asymmetry	LF-HRV HF-HRV Total HRV Coherence Index (CI) Rosenberg Self-Esteem Scale State-trait Anxiety Inventory	Experimental	Significant differences in biofeedback group (HF: z=0.183; p=0.005. LF: z=0.112; p=0.014). IC: z=3.92; p<0.001) Significant changes in TIME x Area x Group, TIME x Group Biofeedback group reveals leveled right frontal asymmetry (and total frontal alpha power) and a shift towards left parietal and occipital alpha asymmetry	23
Brugnera et al. (2017) both	65 Healthy participants (mean age of 24.7, SD= 3.9)	Near infrared spectroscopy (NIRS)	logHFpow Heart Rate	Experimental	Heart rate positively correlated with changes on the right channel of the NIRS in both control (p<0.001) and experimental (p<0.041) groups. Study revealed a increase in PFC areas but no asymmetry during the experimental condition	19
Constantinescu et al. (2018) right	15 right MCA stroke patients (Mean age 59.7; SD=10.3) 15 left MCA stroke patients (Mean age 59.4; SD=8.43) 15 healthy participants (Mean age 59.33; SD=7.28)	CT or MRI of lesion (stroke within 6 months of the study)	LFnu HFnu RR SD1 (fast beat-to-beat variation) SD2 (long-term variability) SDNN pNN50 RMSSD Heart Rate	Quasi-Experimental	During resting phase - Left stroke group showed higher parasympathetic control (RMSSD and pNN50; p<0.05) than the right stroke group (same in HFnu) and lower LF/HF ratio. pNN50 levels were lower in the right stroke patients compared to control group. Right stroke group revelead higher sympathetic control of HR. During deep breathing phase –	20

					Left stroke group had a more pronounced vagal influence on HR (HFnu and RMSSD) and lower LF/HF. During standing phase – Right stroke group had lower pNN50, SDNN, LFnu and HFnu compared to control.	
Sturm et al. (2018) left	24 Healthy participants and 23 with bvFTD	fMRI	Heart Rate RSA SCL Respiration period Finger temperature	Quasi-Experimental	Smaller left vAI volume and lower vAI- ACC connectivity are associated with lower baseline PNS activity Stronger connectivity in ACC-hypothalamus/amygdala edges relates to lower baseline PNS activity Stronger connectivity in ACC-hypothalamus/amygdala edges relates to higher SNS activity	25
Wei et al. (2018) both	185 Healthy participants (Mean age= 35.19; SD= 14.02)	MRI (voxel-based mapping)	LF-HRV HF-HRV RMSSD	Experimental	Negative correlation between HF-HRV and gray matter on right areas of the brain (putamen, caudate, amygdala, insula, superior temporal gyrus, temporal pole and parahippocampal gyrus) and in bilateral striatal and limbic areas. Similar results to RMSSD	19