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THE RELATIONSHIP BETWEEN THE VAGUS NERVE, AUTISM AND GENOMIC NEUROSCIENCE: UNLOCKING THERAPEUTIC POTENTIAL

Fabiano de Abreu Agrela Rodrigues
https://orcid.org/0000-0003-0112-2520

Luiz Felipe Chaves Carvalho
https://orcid.org/0000-0003-3777-5910

Elodia Avila
https://orcid.org/0009-0007-0195-0277

Clara Amorim Ferreira Amaral
https://orcid.org/0009-0008-0300-904X

Velibor Kostić
https://orcid.org/0009-0009-0196-1288

Abstract: Autism Spectrum Disorder (ASD) is often accompanied by difficulties in social behavior and emotion regulation, potentially associated with dysfunctions of the autonomic nervous system. Vagus nerve stimulation (VNS), a neuromodulation technique used in epilepsy and depression, has shown promise in improving behavior in individuals with ASD. This review examines the existing literature on the effects of VNS on behavior in ASD, finding preliminary evidence of its potential benefits, regardless of its effects on seizure frequency and mood. However, more rigorous studies are needed to confirm these findings.
Keywords: Autism Spectrum Disorder, Vagus Nerve Stimulation, Autonomic Nervous System, Social Behavior, Emotion Regulation

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex, multifactorial neurodevelopmental disorder characterized by persistent deficits in social communication and interaction, as well as restricted and repetitive patterns of behaviour, interests or activities. Growing evidence suggests that dysfunction of the autonomic nervous system (ANS), responsible for regulating physiological and emotional functions, plays an important role in the pathophysiology of ASD. The vagus nerve, the tenth cranial nerve and the main component of the parasympathetic nervous system, has been shown to be a promising therapeutic target for modulating ANS activity and potentially alleviating ASD symptoms. Vagus nerve stimulation (VNS), a neuromodulation technique already approved for epilepsy and depression, has emerged as a promising intervention to modulate vagal activity and improve emotional regulation in individuals with ASD. In parallel, genomic neuroscience seeks to identify genetic variants that may influence the development and function of the vagus nerve, contributing to the understanding of the molecular mechanisms of ASD and the development of personalized therapies.

DEVELOPMENT

The autonomic nervous system (ANS) plays a crucial role in regulating the body's responses to stress and environmental changes. In neurodivergent individuals, such as those with Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD), the ANS often shows a pattern of rigidity, resulting in a reduced window of tolerance to stress and challenges in adapting to new situations.

VAGUS NERVE: THE KEY TO REGULATION

The vagus nerve, the tenth cranial nerve and the most extensive of the parasympathetic nervous system, has emerged as a central component in the understanding and potential treatment of neurodivergence. Vagal activity, as measured by heart rate variability (HRV), correlates with emotional regulation capacity and resilience to stress. Studies have shown that children and adults with ASD and ADHD have, on average, reduced vagal tone, which suggests a lower capacity to adapt and recover from challenges.

THERAPEUTIC IMPLICATIONS AND GENOMIC NEUROSCIENCE

Understanding the relationship between the vagus nerve and neurodivergence opens the door to new therapeutic approaches. Interventions aimed at modulating vagal activity, such as breathing exercises, exposure to cold, meditation and even taking probiotics have shown promise in improving emotional regulation and expanding the window of tolerance in neurodivergent individuals.

Transcutaneous VNS (tVNS): Recent studies highlight that tVNS, applied to the auricular branch of the vagus nerve, can significantly improve ASD symptoms, such as emotional regulation and anxiety reduction. tVNS has been shown to activate brain regions associated with ASD and produce therapeutic effects for both core ASD symptoms and comorbidities such as epilepsy and depression (Jin & Kong, 2017).

VNS and Epilepsy: In addition, VNS has shown significant benefits in patients with ASD and intractable epilepsy. Research indicates improvements in patients' quality of life and mood following implantation of the VNS device. These findings suggest that VNS may be an effective therapeutic approach for patients with these comorbid conditions (Levy et al., 2010).

Genomic neuroscience also plays a crucial role in this area, investigating how genetic variants can influence vagal activity and susceptibility to neurodivergence. By identifying genes and molecular pathways associated with vagal tone, genomic research can contribute to the development of personalized and more effective therapies for ASD, ADHD and other neurodivergent conditions.

A PROMISING FUTURE FOR NEUROSCIENCE AND GENOMICS

Research into the vagus nerve and its relationship with neurodivergence represents an emerging and promising field in neuroscience and genomics. By unraveling the neural and genetic mechanisms underlying emotional regulation and adaptation to stress, science is moving closer to a future where personalized and effective interventions could significantly improve the quality of life of neurodivergent individuals (Neff, 2024). Future research should focus on integrating genomic approaches to identify biomarkers that can predict the effectiveness of VNS in ASD patients. Studies indicate that specific genetic variants, such as those in adenosine kinase genes, can influence the response to VNS treatment, suggesting a path towards more personalized therapies (Zhang et al., 2021). In addition, the application of connectomics techniques can help map the neural networks involved in the response to VNS, providing valuable insights to optimize stimulation parameters and improve clinical outcomes (Hachem et al., 2018). The combination of these approaches promises significant advances in the treatment of ASD and other neurodivergent conditions.

Although this article highlights the importance of genomic neuroscience in identifying genetic variants associated with the vagus nerve and Autism Spectrum Disorder (ASD), further discussion is needed to better understand the molecular mechanisms involved. Research has identified several genes and molecular pathways that can influence the function of the vagus nerve, offering indicators of ASD susceptibility and possible therapeutic approaches. For example, variants in the **CHRNA7** (nicotinic acetylcholine receptor) and **HCN2** (hyperpolarization-activated ion channel) genes are involved in the regulation of parasympathetic neurotransmission and may influence the effectiveness of vagus nerve stimulation. The variant in the **CHRNA7** gene is associated with dysfunctions in sensory and autonomic processing in individuals with ASD, suggesting that modulation of this pathway may improve the response to VNS treatment. In addition, the **HCN2** gene has been linked to the control of neuronal excitability, and variants in this gene may modify patients' response to VNS, potentially impacting emotional regulation and social behavior. Another pathway of interest is the serotonergic pathway, which is crucial for modulating mood and behavior. Genomic research has shown that variants in the **SLC6A4** gene, which codes for the serotonin transporter, can affect vagus nerve func-

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tion and the response to VNS treatment. Understanding how these variants influence the interaction between the vagus nerve and ASD could lead to the development of more personalized and effective interventions.

VAGUS NERVE STIMULATION (VNS) AS A TREATMENT FOR FEAR AND ANXIETY IN INDIVIDUALS WITH AUTISM SPECTRUM DISORDER (ASD)

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects 1 in 44 children and is commonly accompanied by heightened fear and anxiety responses. Exposure-based cognitive-behavioral therapies (CBTs) have proven effective in treating anxiety disorders in ASD patients, but high relapse rates indicate the need for additional treatment strategies. Vagus nerve stimulation (VNS) has emerged as a promising adjunct to CBTs, with the potential to reduce anxiety and improve the consolidation of extinction memories in individuals with ASD (Shivaswamy et al., 2022).

ENV, approved for use in the treatment of epilepsy and depression, has shown promising results in preclinical studies, accelerating extinction learning and decreasing physiological measures of fear expression in rodents. Additionally, ENV promotes the generalization of extinction memory, making exposure--based therapies more effective and reducing relapse. (Shivaswamy et al., 2022)

The mechanisms by which VNS can treat fear and anxiety in ASD involve increasing neural plasticity in the pathway from the prefrontal cortex to the amygdala, increasing norepinephrine release and modulating plasticity in other regions of the cortex. ENV also has anxiolytic effects, reducing the sympathetic stress response and making exposure-based therapies more tolerable for ASD patients (Shivaswamy et al., 2022).

Chronic VNS can also be beneficial in the treatment of other ASD comorbidities, such as epilepsy and depression. Studies in ASD patients undergoing chronic VNS have shown improvement in seizures, mood, alertness, social functioning and decreased aggression (Shivaswamy et al., 2022).

Although invasive VNS, which requires surgical implantation, is FDA-approved, less invasive approaches, such as the ReStore system and transcutaneous VNS (tVNS), are being investigated to increase the tolerability and efficacy of therapies in ASD patients (Shivaswamy et al., 2022).

NEUROMODULATION OF AUTISM SPECTRUM DISORDER (ASD) USING VAGUS NERVE STIMULATION (VNS)

Growing evidence suggests an important role for the autonomic nervous system (ANS) in social behavior and emotional regulation, skills that are often affected in people with ASD. Vagus nerve stimulation (VNS), a neuromodulation technique already approved for epilepsy and depression, is emerging as a potential therapy for ASD, aimed at modulating autonomic pathways and improving emotional regulation (van Hoorn et al., 2019).

VNS involves implanting an electrode in the neck, stimulating the left vagus nerve. Although the exact mechanisms are not yet fully understood, VNS has been shown to influence brain areas linked to depression and emotional regulation, as well as increasing vagal tone, the release of noradrenaline and serotonin, and levels of brain-derived neurotrophic factor (BDNF), all of which have potential implications for the treatment of ASD. (van Hoorn et al.,2019)

Case studies and case series provide preliminary evidence that VNS can improve behavior in individuals with ASD, independently of the effects on seizure control and mood.

Improvements in quality of life and a reduction in challenging behaviors, such as aggression and self-injury, have been observed in ASD patients undergoing VNS. (van Hoorn et al., 2019)

Although most of the literature reviewed supports the notion that VNS benefits problem behaviors in ASD, the descriptive nature and lack of control groups in existing studies limit definitive conclusions. However, reports of immediate behavioral benefits following VNS activation suggest an effect on emotion regulation, which may be a key mechanism for behavioral improvement in autistic individuals (van Hoorn et al., 2019).

VAGUS NERVE STIMULATION AND ASD: A NEW THERAPEUTIC PERSPECTIVE

Recent evidence suggests that individuals with Autism Spectrum Disorder (ASD) have decreased resting vagal activity and reduced vagal reactivity to social and emotional stimuli (BREIT et al., 2018). This dysfunction of the vagus nerve, the longest of the cranial nerves and a central component of the parasympathetic nervous system, has been associated with a variety of symptoms, including anxiety, irritability, difficulties in emotional regulation and problems in social interaction (BREIT et al., 2018). Vagus nerve stimulation (VNS), a non-invasive treatment, has shown promise in preliminary studies, suggesting benefits in social communication, emotional regulation and adaptive behavior in people with ASD (BREIT et al., 2018). Additionally, ENV can positively impact social skills and communication in individuals with ASD, in addition to modulating brain areas associated with the neuropathology of the disorder and immune function, which is often compromised in ASD (Jin and Kong, 2017). Genomic neuroscience has identified genetic variants that can influence the development and function of the vagus nerve, increasing the risk of ASD and contributing to vagal dysfunction and autism symptoms (BREIT et al., 2018). The assessment of vagus nerve function through heart rate variability (HRV) and the application of stimulation therapies, such as targeted chiropractic adjustments or transcutaneous vagus nerve stimulation (tVNS), represent promising strategies to improve the quality of life of people with ASD (Ebel, 2024; Jin and Kong, 2017). However, more research is needed to elucidate the mechanisms underlying the relationship between the vagus nerve and ASD, and to establish effective and personalized treatment protocols.

CONCLUSION

Research into the relationship between the vagus nerve and Autism Spectrum Disorder (ASD) opens up a promising field for the development of new therapeutic approaches. The modulation of vagal activity, whether through invasive techniques such as ENV or non-invasive techniques such as tVNS, shows promise in improving symptoms such as anxiety, difficulties in emotional regulation and problems in social interaction. Genomic neuroscience offers a path to personalized therapies by identifying genetic variants that influence vagus nerve function and susceptibility to ASD. However, more research is needed to better understand the mechanisms underlying this relationship and establish more effective and individualized treatment protocols, boosting advances in the field of neuroscience and genomics and, consequently, improving the quality of life of individuals with ASD.

Statement of contributions: Rodrigues, F. A. A. was the idealizer, owner and creator of the concept, wrote and revised the manuscript. Guided the team in data collection and revised the manuscript.

REFERENCES

• Breit, S., Kupferberg, A., Rogler, G., & Hasler, G. (2018). Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders. *Frontiers in Psychiatry*, 9, 44.

• Ebel, T. (2024). The Vagus Nerve and Autism: An Overlooked Factor. *PX Docs*.

• ENGINEER, Crystal T. et al. Vagus nerve stimulation as a potential adjuvant to behavioral therapy for autism and other neurodevelopmental disorders. **Journal of Neurodevelopmental Disorders**, v. 9, n. 20, 2017.

• Jin, Y., & Kong, J. (2017). Transcutaneous Vagus Nerve Stimulation: A Promising Method for Treatment of Autism Spectrum Disorders. *Frontiers in Neuroscience, 10*.

• Levy, M., et al. (2010). Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. *Journal of Neurosurgery. Pediatrics, 5*(6), 595-602.

• Neff, M. A. (2024). *The Autistic and ADHD Nervous System*.

• Shivaswamy, T., Souza, R. R., Engineer, C. T., & McIntyre, C. K. (2022). Vagus Nerve Stimulation as a Treatment for Fear and Anxiety in Individuals with Autism Spectrum Disorder. *J Psychiatry Brain Sci*, *7*, e220007.

• van Hoorn, A., Carpenter, T., Oak, K., Laugharne, R., Ring, H., & Shankar, R. (2019). Neuromodulation of autism spectrum disorders using vagal nerve stimulation. *Journal of Clinical Neuroscience*, *63*, 8-12.