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Radio Electric Asymmetric Conveyer (REAC) Epigenetic Neurobiological Modulation for Neuropsychological Disorders in Autism

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FOREWORD:

Some preliminary words are deserved about the REAC (Radio Electric Asymmetric Conveyer) technology that represents a complex and sophisticated therapeutic means for neurobiological modulation, designed to reinstate cellular polarity and rebalance the endogenous bioelectric fields [1-71]. Its therapeutically relevant outcomes in the context of neurological dysfunctions as well on their complex epigenetic traits and features, has by now achieved impressive clinical results, given the widely bespoken eventual deep impact on neuronal and brain connectome dynamics.

1. INTRODUCTION

This work, carried out in the completion of my Ph.D. curriculum, primarily focuses on autism spectrum disorders (ASD) and, in particular, takes into account Radio Electric Asymmetric Conveyer (REAC) modulatory effects on the neurobiological background of epigenetic sign and symptom cohort accompanying ASD.

In the intricate landscape of ASD, a complex neurodevelopmental disorder marked by demanding obstacles and hindrances in communication abilities, social interactions, and behavioral schemes, my research to explores the effects of REAC technology in enhancing these functional abilities.

By delving into this investigation, I hope, also, to significantly support the global understanding of how targeted treatments, such as REAC, can optimize endogenous bioelectrical activity, have a positive impact on the symptoms of ASD and other neuropsychological disorders.

of this research aligns with a broader initiative aimed at advancing knowledge and disseminating insights into the application of REAC itself and, more extensively, of neurobiological modulation therapies in precision medicine as well as in the conceptual emergence of these developing practices into medicine and psychology. It is my strong belief that these efforts will contribute to the evolving landscape of therapeutic interventions in neuropsychological disorders, offering hope for improved outcomes and quality of life.

1.1 Autism

Autism is a complex and diversified neurological [72-74] and neuropsychiatric [75-77] disorder that involves a variety of genetic [78-82] and epigenetic factors [83-87] in its origin. Autism serves as the prototypical manifestation within the broader spectrum of disorders classified as "Pervasive Developmental Disorders" (PDD) or "Autism Spectrum Disorders" (ASD) [88-91].

These disorders share commonalities in deficiencies across linguistic abilities, cognitive functions, and social-behavioral relations.

Within the PDD category, Autism includes distinct subtypes:

- Asperger's Syndrome [92-94], characterized by linguistic and non-nonlinguistic troubles in social interaction with no cognitive impairment or developmental delay in linguistic skills.
- Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) [95, 96], featuring characteristics similar to autism but insufficient for the classical diagnosis.
- Childhood Disintegrative Disorder (CDD) [97-99], a rarer form leading to regression and severe disability after a seemingly normal development period.

Although specific symptoms may become apparent from birth, identifying autism before 24- 36 months is complex. The disorder shows a wide range of clinical presentations with individually defined pathologic stigmas with notable difficulties in social interactions, as well in communication abilities, stereotypic behaviors, and fixed interests. Social interaction impairments [100] are featured by delays in spoken language development with limited expressive flexibility, by difficulties in non-verbal language, in establishing playful bonds with peers, and in interpreting the others' emotions (empathetic skills). [30, 31]

Besides motor stereotypies and repetitions, further peculiar behavioral traits are marked by interests in unusual object details, and engagement in compulsive actions [101, 102].

Additional active or induced behavioral signs observed in autistic individuals include abnormal responses to sensory stimuli [103, 104], reduced sensitivity to pain [105, 106], sleep disorders [107, 108], limited food preferences [109, 110], and motor skill challenges [111, 112].

The causes of autism remain largely unknown, with a complex interplay of genetic and environmental factors [113, 114]. Studies on twins indicate a high concordance in identical twins (monozygotic) [115] compared to non-identical twins (dizygotic) [116], thus supporting a genetic basis [117].

Genetic factors include familial associations, involvement of genes related to neurodevelopment, and certain genetic disorders like Angelman Syndrome [118] and Rett Syndrome [119].

Autism is often comorbid with a flood of other neuropathological or neuropsychological conditions such as learning disorders (as, for instance, dyslexia, dyscalculia, dysgraphia), dyspraxia or ADHD [120, 121], specific neurological syndromes such as Tourette's Syndrome [122], or many forms of inherited epilepsy (genetically or clinically evaluated), or again many neuropsychological disturbances, namely anxiety, depression, bipolar and obsessive-compulsive disorders.

Recognizing that genetic and environmental risk factors are interconnected is crucial, as a specific gene combination may confer susceptibility, and the presence of environmental factors can trigger the manifestation of typical symptoms.

1.2 Autism and epigenetics

Aside from genetic factors (contributing signs in a 40 to 80% of full-blown cases), a complex thread of epigenetic and environmental factors are co-involved in the expressions of autistic spectrum traits [54]. This interplay significantly influences the neurobiological background during critical periods of brain development [85, 123].

Epigenetic mechanisms that may contribute to the origin of autism are identified in DNA methylation [85], histone modifications [124], non-coding RNA [125, 126], geneenvironment interaction [127, 128], maternal stress [129, 130], and prenatal factors [131, 132].

Methylation is a chemical modification involving the addition of methyl groups to DNA, influencing its structure and access to genetic information. Some studies have demonstrated that anomalous methylation patterns may be associated with autism [133-136].

Histones are proteins that wrap around DNA, regulating gene access. Modifications such as histone acetylation and methylation can influence gene expression and may be involved in autism development [124, 137].

The whole constellation of RNAs (snRNA, small nuclear RNAs, micro RNAs, miRNAs, or long /short non-coding, IncRNAs) and related interference processes, (RNAi) play a crucial

role in epigenetics by controlling gene expression at the pre and post-transcriptional level [138]. As it has shown[139] disruptions in the regulation of these RNA types or mechanisms may modulate crucial steps in brain development stages and the related behavioral expressions associated with autism.

The Epigenetic events besides their direct influences, by provoking genic expression disorders can modulate postnatal brain's adverseresponse to environmental factors, making some individuals more susceptible to autism under certain conditions [140].

1.3 Autism and depression

Depression is a mood disorder characterized by persistent feelings of sadness, hopelessness, and worthlessness [141]. The relationship between depression and Autism Spectrum Disorder (ASD) is complex and multifaceted and not fully understood [142, 143], which reflects the intricate interplay of biological, psychological and environmental factors [144]. Although depression is not a core feature of ASD, individuals with ASD often show a higher prevalence of comorbid depressive symptoms than the general population. Studies have found that up to 40% of people with ASD also meet the criteria for a diagnosis of depression [145, 146].

The comorbidity between depression and autism is a topic of particular interest, as it has been consistently observed in various studies[147-149]. In particular, it has been highlighted that the correlation between depression and autism is phenomenologically (non in causal mutuality) bidirectional, with both conditions influencing and exacerbating each other [150, 151]. Moreover individuals diagnosed with depression have been found to show higher rates of autistic traits [152], suggesting a potential shared etiology or overlapping underlying mechanisms. Similarly, individuals with autism are more susceptible to experiencing depressive symptoms due to numerous factors such as social isolation, difficulties in social interaction, and dealing with challenges associated with the disorder.

The relationship between depression and ASD requires consideration of various underlying mechanisms that contribute to the development of the clinical picture:

1) Genetic vulnerabilities: Genetic studies have provided evidence of shared genetic vulnerabilities [153] between depression and autism [154] such as those involving serotonin [155] and dopamine [156] pathways, always implied both in mood and ASD disorders [155, 157]

2) Neurotransmitter Systems: As previously underlined, all of, but still far to be detailed, "complex genic and neurobiological clusters" predisposing to depression may be related to ASD[145].

3) Neurodevelopmental abnormalities: Both depression and autism involve are often associated with disruptions in neurodevelopmental processes [158, 159]. Structural and functional abnormalities in brain regions involved in emotion regulation, such as the prefrontal cortex and amygdala [160, 161], have been observed in individuals with comorbid depression and autism [162, 163].

4) Communication and social challenges: The main features of ASD, including impaired social communication and difficulty forming and maintaining relationships, eventually lead to further social isolation and feelings of loneliness. Persistent challenges in social interactions progressively contribute to spiraling depressive symptoms [164].

5) Cognitive factors: All the previous ASD featuring factors, listed above, are conjugate to widely expressed cognitive failures associated with ASD, such as deficits in executive tasks and repetitive thought patterns, may also contribute to the development of depressive symptoms [165]. Persistent difficulties in adapting to change, managing transitions, and coping with unexpected events can contribute to increased stress and vulnerability to depression.

1.4 Autism and anxiety

The intricate connection**s** between neuropsychological disorders such as anxiety and ASD a neuropathological illness with recognized genic precursors underscore a complex relationship between these two conditions. The sound pinpointing of anxiety signs within the ASD semeiotic frames [166], might be essential for delivering effective support and interventions.

As it has shown in many studies [166], anxiety disorders are more widespread among ASD subjects comparison with the general population. In detail, the well-established comorbidity between anxiety and autism estimates as many as 40% of individuals with autism fulfill the criteria for an anxiety disorder [167]. Recognizing the prevalence and co-occurrence rates is crucial for understanding the impact of anxiety on individuals with autism.

In addition, different forms of anxiety disorders are recognized, such as generalized anxiety disorder [168], social anxiety disorder [169, 170], specific phobias [171], and obsessivecompulsive disorder [172] and each psychological profile has been found variously related with ASD phenomenology [173]. Each anxiety disorder type can pose distinct challenges and affect the daily functioning of individuals with autism in varied ways.

The relationship between anxiety and ASD requires consideration of various underlying mechanisms that contribute to the development of the clinical picture:

1) Cognitive Factors: cognitive elements[174], such as increased focus on potential threats, a lack of tolerance for uncertainty, and rigidity in thinking, have been identified as common factors in both anxiety and autism. These cognitive processes might play a role in the emergence and persistence of anxiety symptoms among individuals with autism.

2) Sensory Processing Differences: many individuals with autism often experience sensory processing variations, which could be a factor in the manifestation of anxiety symptoms [175, 176]. The anxiety responses in people with autism may be enhanced by increased sensitivity to sensory stimuli or sensory overload [177]. By comprehending the dynamic relationship between sensory processing variances and anxiety, it becomes possible to develop interventions based on sensory approaches to mitigate anxiety symptoms.

3) Social and Communication Challenges: The social and communication difficulties [178] core ASD aspects understandably contribute to the onset of anxiety. Challenges in comprehending and navigating social interactions, interpreting social cues, and encountering social rejection may precipitate growing anxiety levels in individuals with autism.

1.5 Autism and internalizing disorders

Internalization disorders encompass a broad spectrum of conditions, such as emotional distress [179, 180], depressive disorders, asthenia, negative affectivity, anxiety disorders, dysthymia, somatic disorders (ailments that can afflict any part and function of the body with various manifestations, especially diffuse and migratory pains, and various difficulties), obsessive-compulsive and related disorders, trauma and stress-related disorders, including post-traumatic stress.

Also included in internalization disorders are social withdrawal, sadness, decreased academic and occupational performance, bulimia, anorexia, and dissociative disorders or discontinuity in the normal integration of consciousness, memory, identity, perception, body representation, and behavior.

In general, in internalization disorders, somatic disorders, consisting of a wide range of unexplained physical symptoms, as defined in contemporary medicine, often represent the initial symptoms, which, due to their nature, show little or no improvement with pharmacological treatments.

Internalization disorders constitute the "unperceivable" background exacerbating all disorders and diseases, including those in developmental age, such as various forms of dyslexia, language disorders, attention deficit hyperactivity disorder (ADHD), and autism [165].

Internalization disorders originate in the individual's difficulty in generating adaptive responses suitable for the environmental situation in which one lives.

At the biological level, this adaptive difficulty originates and is sustained through imbalances in cellular bioelectrical activity. Over time, these imbalances can lead to epigenetic changes and may become heritable modifications.

There are several factors that can contribute to the onset of internalizing disorders:

1) Neurobiological Factors: studies suggests that imbalances in neurotransmitters and neuromodulators, such as serotonin [181, 182], norepinephrine, and dopamine[183], contribute to the development of internalizing disorders. For instance, decreased serotonin levels are often associated with depressive disorders. Additionally, structural and functional abnormalities in specific brain regions involved in emotion processing, memory, and stress regulation, like the amygdala, the hippocampus, and the prefrontal cortex, have been linked to internalizing disorders.

2) Genetic Influences: evidence supports a genetic component in the susceptibility to internalizing disorders. Individuals with a family history of depression or anxiety may be at a higher risk of developing these conditions. Furthermore, gene-environment interactions, where genetic predispositions interact with environmental factors like early life stress or trauma, can contribute to the manifestation of internalizing disorders.

3) Cognitive Factors: cognitive biases, including negative interpretations of events, low selfesteem, and a tendency to focus on perceived threats, are often observed in individuals with internalizing disorders [165]. Cognitive models emphasize the role of distorted thinking patterns in the development and maintenance of these disorders. Furthermore, rumination, which is prolonged and repetitive negative thinking, is particularly associated with depression.

4) Psychosocial Factors: adverse experiences during childhood, such as abuse, neglect, or insecure attachment, may contribute to the development of internalizing disorders later in life. Additionally, major life stressors like loss, trauma, or chronic stress can trigger or exacerbate these disorders [184]. The lack of social support or poor social functioning can contribute to the onset and maintenance of internalizing disorders [179, 185].

2. ENDOGENOUS BIOELECTRICAL ACTIVITY

Bioelectricity is a fundamental aspect of biology that pertains to the generation, transmission, and utilization of electrical and electrochemical) signals within biological systems. It encompasses a collection of electrically driven phenomena observable in living organisms[186, 187].

Bioelectricity arises from the collective endogenous cellular activities produced by individual cellular components. These activities concur with ionic currents, thereby giving rise to cellular bioelectricity [188].

Endogenous bioelectrical activity [59, 189], a manifold form of cellular communication, has been recognized for its integral role in various biological processes, from embryogenesis and tissue regeneration to behavior and cognition. The intricate interplay between endogenous bioelectrical signals, epigenetic modifications, and neurodevelopment may offer novel insights into neurodevelopmental disorders like Autism Spectrum Disorder (ASD).

2.1 Interplay of Endogenous Bioelectrical Activity, Epigenetic, Neurodevelopment and Autism Spectrum Disorder

2.1.2 Endogenous Bioelectrical Activity and Neurodevelopment

Endogenous bioelectrical activity refers to the spontaneous electrical currents produced within an organism, primarily driven by ion channels, pumps, and gap junctions across the cell membrane [190]. These bioelectrical signals orchestrate a multitude of developmental processes, including cell differentiation, migration, and synaptic formation. In the context of neurodevelopment, bioelectrical signaling plays a crucial role in the patterning of neural circuits, guiding the proliferation and migration of neurons, the formation of synapses, and the establishment of functional neuronal networks [187, 191].

2.1.3 Epigenetics and Neurodevelopment

Epigenetics, the study of heritable changes in gene expression that do not involve alterations to the underlying DNA sequence, also holds significant implications for neurodevelopment.

Epigenetic modifications, including DNA methylation, histone modification, and noncoding RNA molecules, dynamically regulate gene expression and thus influence neuronal differentiation, maturation, and synaptic plasticity[87, 192]. The epigenetic landscape is particularly susceptible to environmental factors, suggesting that external influences may indirectly impact neurodevelopment through epigenetic alterations[193, 194].

2.1.4 Interplay of Endogenous Bioelectrical Activity and Epigenetics

Recent research suggests a profound interaction between endogenous bioelectrical activity and epigenetic mechanisms [195, 196]. Bioelectrical signals can modulate epigenetic states, thereby influencing gene expression and cellular behavior [188]. Conversely, epigenetic modifications can alter the expression of ion channels and other bioelectric machinery, thereby influencing bioelectrical cues [197]. This bidirectional relationship creates a complex regulatory network that plays a key role in neurodevelopment[198].

2.1.5 Endogenous Bioelectrical Activity, Epigenetics and Autism Spectrum Disorder

Autism Spectrum Disorder is characterized by a range of neurodevelopmental impairments, including social communication difficulties and repetitive behaviors. Emerging evidence suggests that both aberrant endogenous bioelectrical activity and atypical epigenetic modifications may contribute to the pathogenesis of ASD[199].

Bioelectric abnormalities, such as altered ion channel function or dysregulated bioelectrical signaling, could disrupt the normal patterning of neural circuits, leading to the neurodevelopmental anomalies seen in ASD[200-203]. Similarly, epigenetic disruptions in ASD, such as aberrant DNA methylation [204, 205] or histone modification patterns, could dysregulate key neurodevelopmental genes, further contributing to ASD pathology [124, 206].

In particular, the interplay between bioelectrical activity and epigenetics may be critical in ASD[207]. Dysregulated bioelectrical signaling could induce aberrant epigenetic changes, leading to abnormal gene expression and neurodevelopment [208, 209]. Conversely, atypical epigenetic landscapes in ASD could alter bioelectric machinery expression, thereby disrupting bioelectrical cues and neurodevelopment [210].

3. RADIO ELECTRIC ASYMMETRIC CONVEYER (REAC) TECHNOLOGY

The Radio Electric Asymmetric Conveyer (REAC) is an innovative technology designed to restore cellular polarity and harmonize the endogenous bioelectric field[47, 65]. It has shown promise in addressing neurological dysfunctions and impacting neural communication mechanisms. Unlike conventional electric circuits with dual poles, REAC operates on an asymmetrical circuit with a single physical pole. This unique design acts as an attractor for currents induced in the body by radio electric fields asymmetrically conveyed. REAC technology operates by generating a low-intensity radio electric field. This field interacts with biological tissues, creating radio electric gradients. These gradients play a crucial role in re-establishing ion flows that have been disrupted or altered.

Essentially, REAC technology utilizes the underlying principles of energy and charge to restore the natural ion balance in biological systems, potentially contributing to the maintenance of physiological allostasis. This process is a key aspect of the body's response to various physiological conditions and can have significant implications for health and disease management. The various and specific therapeutic protocols of the technology have demonstrated significant biological effects, working to restore cellular polarity and support normal cell function. By rebalancing the endogenous bioelectric field, it has the potential to rectify neural communication dysfunctions associated with neurological disorders.

In the field of neuromodulation therapies, REAC stands out as a promising alternative. It has been explored through specific treatment protocols, particularly in cases where traditional pharmacological interventions have been ineffective, such as in neurodegenerative diseases [34, 35, 42, 70]. REAC technology also shows potential in treating neuropsychological disorders like Autism Spectrum Disorder (ASD) [51, 69, 211]. Research has investigated its benefits in alleviating depression [2, 6, 16, 45, 49, 50], anxiety [6, 11, 16, 45, 49, 50], and stress in specific subpopulations [1, 4, 6, 12, 17, 20, 45, 49, 50, 58, 211, 212].

Furthermore, specific REAC treatments have demonstrated effectiveness in restoring tissue and organ function [213], healing wounds, particularly in difficult conditions such as pressure ulcers and burns [54]. Overall, REAC technology represents a significant advancement in neuromodulation therapies. Its ability to restore cellular polarity and harmonize the endogenous bioelectric field, substantiates the technique wide range of effects, from neuropathological and neuro psycho pathological disorders to tissue reparation. Further research**es** will provide further results in REAC technology application.

3.1 REAC Neurobiological Treatment Protocols

3.1.1 Neuro Postural Optimization Treatment

The human body is an intricate system that relies on a delicate balance of neural communication to maintain its posture, coordination, and overall well-being. Any disruption to this delicate balance can lead to a range of functional impairments, affecting movement, balance, and even cognitive performance.

In recent years, the REAC Neuro Postural Optimization (NPO) treatment has emerged as a promising approach for addressing these neuro psycho motor dysfunctions[33, 57, 58].

The REAC NPO treatment, aims to restore optimal postural alignment and movement patterns. It involves a single brief session, typically lasting just a few milliseconds, during which the REAC probe is gently applied to the ear concha. This short intervention has been shown to induce neuroplastic changes within the brain, leading to improved postural control and reduced reliance on compensatory strategies [33, 57]. The significance of NPO treatment extends beyond its immediate impact on posture. Studies have demonstrated that it can also have positive effects on a range of other functional domains, including:

Motor Control: NPO has been shown to enhance motor coordination and reduce tremors, improving fine motor skills and gait stability.

Pain Management: NPO has been associated with reduced pain perception and improved pain tolerance, offering potential relief for individuals with chronic pain conditions.

Cognitive Function: NPO has been shown to enhance cognitive performance, particularly in domains related to attention, memory, and task switching[58].

Quality of Life: Overall, NPO has been shown to significantly improve quality of life by reducing functional limitations and enhancing daily activities[68, 70].

The potential of NPO treatment is increasingly recognized by the medical community, with its use expanding to address a variety of conditions, including:

Neurological Disorders: Parkinson's disease, dystonia, and stroke-related impairments

Mental Health Conditions: Anxiety, depression, and post-traumatic stress disorder

Pediatric Conditions: Developmental delays, autism spectrum disorders, and attention deficit hyperactivity disorder (ADHD)

General Well-being: Improving overall balance, coordination, and cognitive function.

3.1.2 Neuro Psycho Physical Optimization (NPPO) treatments

Since their recognition in biological tissues, both in adult animals morphologic and functional maintenance and in shaping the embryological stages endogenous bioelectrical activities (EBA) a critical factor influencing a broad range of physiological and cognitive processes. This intricate network of bioelectrical signals generated within the nervous system plays a fundamental role in regulating neurotransmission, neuroplasticity, and epigenetic mechanisms, all of which are essential for maintaining optimal brain health and function. Within this burgeoning area, REAC Neuro Psycho Physical Optimization treatments (NPPO) have emerged as a novel non-invasive neuromodulation technique that harnesses the power of EBA modulation to address a diverse spectrum of neurological and psychiatric disorders.

Unlike conventional neuromodulation approaches that target specific neural pathways, REAC NPPOs adopt a comprehensive approach, aiming to optimize EBA patterns across various organizational levels, from the cellular to the systemic levels. At the core of NPPOs lies the fundamental principle that alterations in EBA significantly contribute to the development and manifestation of various neurological and psychiatric disorders. By effectively modulating EBA, REAC NPPOs aim to restore balance and harmony within the nervous system, thereby promoting overall well-being.

REAC NPPOs stands in sharp contrast to other therapeutic approaches that often target specific symptoms or disorders in isolation. Instead, REAC NPPOs embraces a comprehensive perspective, recognizing the interconnectedness of the nervous, physical, and psychological systems. This integrated approach acknowledges that disturbances in EBA (Emotional-Behavioral-Attentional) can manifest in various domains, including cognitive function, motor control, sensory processing, and emotional regulation. REAC NPPOs embodies the principles of precision medicine, acknowledging that each individual's EBA profile is unique, ensuring a personalized approach to neuromodulation.

A hallmark of REAC NPPOs is its non-invasive nature, eliminating the need for surgery or implanted devices. This feature makes REAC NPPOs an attractive option for individuals who may be averse to invasive procedures or have concerns about potential side effects. REAC NPPOs represents a transformative paradigm shift in neuromodulation, offering a non-invasive, personalized, and comprehensive approach to addressing a multitude of neurological and psychiatric conditions. With ongoing research and advancements in REAC

technology, this novel therapeutic approach holds immense promise for revolutionizing the treatment landscape for a wide spectrum of disorders.

4. METHODS AND REULTS

I carried out three studies on the potential of Radio Electric Asymmetric Conveyor (REAC) technology to modulate the epigenetic landscape and ameliorate neuropsychological disorders, particularly autism spectrum disorder (ASD).

The researchs examined the effects of REAC neurobiological modulation NPO and NPPO/NPPO-CB on various aspects of ASD, including motor skills, cognitive function, social behavior, and sensory processing.

The findings of the research suggest that REAC NPO and NPPO/NPPO-CB treatments may have a beneficial impact on individuals with ASD.

Specifically, the studies demonstrated enhancements across various domains, including gross motor skills (such as sitting, standing, walking, running, jumping, lifting, and kicking) and fine motor skills (like holding a pencil or scissors, writing, cutting, threading beads, playing with Legos, and buttoning up a coat). Moreover, improvements were observed in language production (pragmatics, grammar, semantics, syntax, phonology, and morphology in both oral and written language) and comprehension (difficulty understanding abstract language, such as idioms or metaphors, difficulty grasping the main idea or themes in reading materials, difficulty making connections between different parts of a text), attention span, concentration, executive functions (such as problem solving, planning, organizing), selfregulation, and social interactions. These social interactions encompassed challenges related to verbal and nonverbal skills, understanding social cues, empathy, and displaying repetitive behaviors. Additionally, the study identified a decrease in stereotypical behaviors and sensory sensitivities.

Overall, the research provides evidence supporting the potential of REAC NPO and NPPO/NPPO-CB treatments as a promising treatment approach for ASD.

For the first study, I have developed a novel assessment tool called the "Autism Profiling Questionnaire (APQ)" specifically designed to evaluate therapeutic outcomes in individuals with ASD. Unlike traditional diagnostic measures, the APQ offers a structured approach for collecting data from caregivers or parents of children with ASD, focusing on the assessment of motor, cognitive, and behavioral deficits commonly associated with the condition.

The APQ comprises 21 carefully crafted questions or items, strategically grouped into three clusters: motor skills, cognitive skills, and behavioral symptoms. Table 1 in this study provides a comprehensive overview of the APQ items and their corresponding clusters.

In this research endeavor, caregivers of children diagnosed with ASD were tasked with rating each item on a scale ranging from 0 to 10, indicating the extent to which the particular skill or behavior was expressed.

This approach allowed for a nuanced evaluation of therapeutic progress and provided valuable insights into the efficacy of interventions tailored to address the multifaceted challenges presented by ASD.

Participants

The study included 112 children with ASD, with an average age of 5.96 years (SD = 3.15) years). There were 26 girls (age = 7 years, $SD = 3.41$ years) and 86 boys (age = 5.65 years, $SD = 3.01$ years). All participants had a previous diagnosis of ASD made by a child psychiatrist using the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R). The children's caregivers opted to add REAC neuromodulation treatments to their existing treatment plans.

REAC Neuromodulation Treatments: This study investigated the effects of two REAC neuromodulation treatments: NPO and NPPO/NPPO-CB. NPO is a single-session treatment designed to improve motor control and treat functional dysmetria (FD). NPPO/NPPO-CB is a cycle of 18 sessions designed to optimize the individual's response to environmental stressors.

Measures: The effectiveness of the REAC neuromodulation treatments was assessed using an evaluation of Functional Dysmetria (FD) and the Autism Profiling Questionnaire (APQ). FD is an asymmetry in muscle activation that is associated with dysfunction of the cerebellum.

Study Timepoints: The study included the following timepoints: T0: APQ administration; T1: Dysmetria assessment; T2: NPO administration; T3: FD assessment after NPO; T4: NPPO/NPPO-CB administration; T5: FD assessment at follow-up; T6: APQ assessment at follow-up.

Effects: the efficacy of two neuromodulation treatments, the neuro postural optimization (NPO) and neuro psycho physical optimization (NPPO/NPPO-CB) treatments, on the modulation of motor, cognitive, and behavioral deficits in children with autism spectrum disorder (ASD). The data shows significant improvements in the APQ scores for all three clusters (motor skills, cognitive skills, and behavioral skills and symptoms) following the and treatments. The disappearance of functional dysmetria (FD) was observed in 100% of the children immediately after the NPO treatment and was stable at 3-month follow-up. No adverse events were reported.

Motor Skills: Figure 1 illustrates the significant improvement in both gross and fine motor skills over time. Specifically, median values for gross motor skills increased from 6 to 7 at T6, indicating substantial enhancement. Similarly, fine motor skills showed improvement, with median values rising $4.5 \rightarrow 6$ from T0 at T6.

Figure 1. Gross and fine motor skills show an improvement with statistical significance p < 0.05

Cognitive Skills: Language production skills exhibited a remarkable improvement, as evidenced by statistical data a median value increase $4 \rightarrow 6$ from T0 at T6 (Figure 2).

Substantial improvements were observed in language comprehension skills with median values rising $5 \rightarrow 6$ from T0 at T6 (Figure 2).

Attention and concentration improved significantly, with median value $5 \rightarrow 6$ from T0 at T6 (Figure 2).

Learning and memory improved significantly, with median values increasing $5 \rightarrow 6$ from T0 at T6 (Figure 2).

Executive functions improved significantly, with median values increasing $5 \rightarrow 6$ from T0 at T6 (Figure 2).

Personal autonomy - Pathological Demand Avoidance (PDA), improved significantly, with median values increasing $4 \rightarrow 6$ from T0 at T6 (Figure 2).

Sphincteric control improved significantly, with median values increasing $5 \rightarrow 9$ from T0 at T6 (Figure 2).

Night rest improved significantly, with median values increasing $6 \rightarrow 8$ from T0 at T6 (Figure 2).

Sensory issues (over-sensitive or under-sensitive to specific sights, sounds, smells or textures) improved significantly, with median values increasing $5 \rightarrow 7$ from T0 at T6 (Figure 2).

Figure 2. Cognitive skills show an improvement with statistical significance $p < 0.05$

Behavioral Skills and Symptoms: Nonverbal communication skills improved significantly, with median values increasing from $5 \rightarrow 7$ from T0 at T6 (Figure 3).

Voluntary eye movements and eye contact improved significantly, with median values increasing $5 \rightarrow 8$ from T0 at T6 (Figure 3).

Adaptation to changes improved significantly, with median values increasing $5 \rightarrow 6$ from T0 at T6 (Figure 3).

Ability to follow social rules in an interaction improved significantly median values increasing $4 \rightarrow 5$ from T0 at T6 (Figure 3).

Interest in socialization and social contact improved significantly, median values increasing $5 \rightarrow 6$ from T0 at T6 (Figure 3).

Figure 3. Behavioral skills show an improvement with statistical significance $p < 0.5$

Self-aggressive behaviors were significantly reduced, with the median value decreasing from 2 to 1 at T6 (Figure 4).

Hetero-aggressive behaviors were significantly reduced, with the median value decreasing from 2 to 1 at T6 (Figure 4).

Agitation and hyperactivity were significantly reduced, with median values decreasing from 6 to 5 at T6 (Figure 4).

Irritability and oppositional behaviors were significantly reduced, with median values decreasing from 6 to 5 at T6 (Figure 4).

Stereotyped behaviors were significantly reduced, with median values decreasing from 5 to 4 at T6 (Figure 4).

Figure 4. Behavioral symptoms show an improvement with statistical significance $p < 0.5$

Suggest that REAC NPO and NPPO/NPPO-CB neurobiological modulation treatments may have a beneficial impact on individuals with ASD. Specifically, the study shows improvements in gross and fine motor skills, language production and comprehension, attention and concentration, executive function, self-regulation, and social interactions. Additionally, the study found a reduction in stereotypical behaviors and sensory sensitivities. The significant improvements observed across all domains of the APQ suggest that these treatments may have a substantial impact on the overall quality of life for individuals with ASD.

In my second study, I employed REAC neuromodulation treatments to quantify and alleviate the impact of stress in ASD using the ATEC test, one of the most widely used tests to evaluate the efficacy of a treatment in individuals with ASD[60].

Population study: The study involved 46 children with a prior diagnosis of autism spectrum disorder (ASD) confirmed through the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). None of the participants were receiving any medication. The group consisted of 12 females (average age of 9.00 ± 4) and 34 males (average age of 10.15 ± 4.57). The overall average age was 9.85 ± 4.42 .

Procedure: Prior to initiating the REAC neuromodulation treatments, the children's caregivers completed the Autism Treatment Evaluation Checklist (ATEC) at baseline (T0). Following the administration of the first REAC NPO treatment (T1), the NPPO/NPPO-CB treatment cycle commenced. This included 18 sessions administered over a period of approximately three weeks. The second ATEC was completed at three months post-treatment (T3).

Evaluation methods: The primary outcome measure was the ATEC, a standardized questionnaire designed to assess the severity of various aspects of ASD across four subtests: speech/language communication, sociability, sensory/cognitive awareness, and health/physical/behavior. Each subtest encompasses a specific set of items, with scores ranging from 0 to 100, indicating the level of ASD severity.

The comprehensive analysis of the ATEC scores revealed significant improvements in all four subtests following the REAC NPO and NPPOs treatment cycle. The percentage of participants with measurable improvements ranged from 69.57% to 89.13% across the subtests.

For the subtest speech/language communication, the comparison of the scores showed that a single REAC NPO and NPPOs treatment cycle was effective in 69.57% of participants with ASD, with $p < 0.005$. This implies that in 32 participants, the parents or caregivers appreciated an improvement in their children with ASD, whereas, in 14 participants, a single treatment cycle was not sufficient to determine an improvement perceivable by parents or caregivers. In particular, the median ATEC value moves from the sixth to the fourth centile, as shown in Figure 5.

Figure 5. Illustrates the distribution of ATEC scores before and after the NPPOs treatment, highlighting a significant shift in the median ATEC value from the sixth to the fourth centile.

As indicated by the sociability subtest, we achieved significant improvements in 84.78% of the participants with ASD following a single REAC NPO and NPPOs treatment cycle Figure 2. This translates to 39 participants exhibiting noticeable improvements in their children's social interactions, while only 7 participants did not demonstrate significant changes. This positive impact is clearly demonstrated in Figure 6, where the median ATEC value shifts from the sixth to the third centile.

Figure 6. Depicts the distribution of ATEC scores before and after the NPPOs treatment, showcasing a noticeable shift in the median ATEC value from the sixth to the third centile. This shift suggests a substantial improvement in communication and interaction abilities among the participants.

The sensory/cognitive awareness subtest showed the most significant improvement among all four subtests, with 78.26% of participants experiencing measurable benefits. This translates to 36 participants exhibiting positive changes in this domain, while 10 participants did not experience sufficient improvement after a single treatment cycle. The median ATEC value for sensory/cognitive awareness shifted from the fourth to the second centile, demonstrating a substantial reduction in the severity of ASD symptoms in this sensory/cognitive awareness subtest (Figure 7).

Figure 7. Clearly depicts the distribution of ATEC scores before and after the NPPOs treatment, demonstrating a remarkable shift in the median ATEC value from the fourth to the second centile.

The health/physical/behavior subtest demonstrated the most effective widespread positive impact, with 41 participants showing noticeable improvements following a single REAC NPO and NPPOs treatment cycle (89.13% effectiveness). This suggests that the intervention effectively addressed the health-related aspects of ASD, as perceived by parents or caregivers. Only 5 participants did not exhibit significant improvement, indicating that the treatment was not universally effective in this domain (Figure 8).

Figure 8. Clearly depicts the distribution of ATEC scores before and after the NPPOs treatment, demonstrating a remarkable shift in the median ATEC value from the sixth to the third centile.

A comprehensive analysis of the ATEC global scores which encompass the sum of the subtest scores, revealed significant improvements in 45 of the 46 participants (98.83%). These improvements were statistically significant ($p < 0.005$). Moreover, the global average score on the ATEC rating scale decreased from the seventh to fifth centile, from 64.17 to 45.54. This remarkable shift in scores is evident in Figure 9.

Figure 9. Presents a compelling visual representation of the ATEC global scores before and after the NPPOs treatment, demonstrating a remarkable shift in the global average score from the seventh to the fifth centile.

The significant improvements observed in the ATEC scores can be attributed to REAC treatments' ability to fundamentally restructure brain activation patterns, fostering greater efficiency, specificity, and competency within activated regions [33, 36]. This neuromodulation effect empowers NPPOs treatments to enhance individuals' ability to cope with environmental stressors and effectively manage the neurocognitive and behavioral consequences of exposome pressure and allostatic overload induced by the COVID-19 pandemic among participants with ASD.

This study provides compelling evidence that a single cycle of REAC NPO and NPPOs treatments can produce clinically meaningful improvements in the core symptoms of ASD across various domains of functioning.

In the third study, I aimed to assess the improvement of functional abilities in children and adolescents with ASD using REAC NPPO treatments and the Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) [69].

The PEDI-CAT assesses a comprehensive range of activities of daily living (ADLs), encompassing 68 elements distributed across four distinct content domains: Getting Dressed, Keeping Clean, Home Tasks, and Eating and Mealtime. The assessment utilizes a 4-point Difficulty Scale, with response options ranging from 'unable' to 'easy', to evaluate children's and adolescents' abilities.

It is utilized both in diagnostic phases and during pediatric rehabilitation evaluations, offering a precise assessment of children's abilities in various contexts such as home, school, and community.

The study included children and adolescents aged 3 to 21 years with a prior diagnosis of autism confirmed by the Autism Diagnostic Interview-Revised (ADI-R). Participants were required to have functional abilities comparable to those of a child between 6 months and 7 years of age.

The study enrolled 27 children and adolescents between 3 and 17 years of age. There were 24 males (mean age: 6.71 years) and 3 females (mean age: 5.67 years).

The assessments were performed before and after the REAC Neuro Postural Optimization (NPO) and Neuro Psycho Physical Optimization (NPPOs) neuromodulation treatments, with a follow-up conducted approximately 3-4 months after the treatments.

The application of the NPO treatment resulted in a rapid and enduring resolution of functional dysmetria (FD) symptoms, with sustained improvement evident at the 3-4 month follow-up evaluation.

The PEDI-CAT results demonstrated a statistically significant improvement in ADL performance, with $p < 0.5$. Figure 1 visually depicts the substantial difference in mean scores between the pre-treatment and follow-up assessments, highlighting the overall enhancement in ADL functioning.

Figure 10. Depicts a substantial improvement in activities of daily living (ADL) domain scores between pre-intervention and follow-up evaluations, indicating a positive impact of the intervention on ADL performance.

The PEDI-CAT Mobility domain encompasses 75 items organized into four distinct categories: Basic Movement & Transfers, Standing & Walking, Steps & Inclines, and Running & Playing. Children and adolescents' capabilities in each category are assessed using a 4-point Difficulty Scale, ranging from 'Unable' to 'Easy'. Our findings revealed a statistically significant difference ($p < 0.05$) between the mean scores obtained before and after the intervention, demonstrating substantial improvements in mobility (Figure 11).

Figure 11. Graphically depicts the substantial improvement in the mobility domain, as evidenced by the significant increase in average scores between pre-intervention and follow-up evaluations.

The Social/Cognitive domain of the PEDI-CAT is composed of 60 items categorized into four distinct areas: Interaction, Communication, Everyday Cognition, and Self-Management. Children and adolescents' abilities within each area are assessed using a 4 point Difficulty Scale, ranging from 'Unable' to 'Easy'. Our findings revealed a statistically significant difference ($p < 0.05$) between the mean scores obtained before and after the intervention, demonstrating notable improvements in social cognition (Figure 12).

Figure 12. Presents a compelling illustration of the substantial improvement in social cognition domain scores observed between pre-intervention and follow-up evaluations, effectively demonstrating the positive impact of the intervention on social cognition skills.

The Responsibility domain of the PEDI-CAT assesses a young person's ability to manage complex life tasks essential for independent living across four distinct areas: Organization & Planning, Taking Care of Daily Needs, Health Management, and Staying Safe. This domain demands the coordination of multiple functional skills, making it a more challenging area of assessment. Accordingly, it is administered to children and adolescents between the ages of 3 and 21 years. The Responsibility domain utilizes a unique 5-point Responsibility Scale, ranging from: adult/caregiver has complete responsibility; the child assumes no responsibility' to 'Child independently takes full responsibility without any form of direction, supervision, or guidance from an adult/caregiver. Our findings revealed a statistically significant difference ($p < 0.05$) between the mean scores obtained before and after the intervention, demonstrating notable improvements in responsibility-related skills (Figure 13).

Figure 13. Evidence of Substantial Improvement in Responsibility Skills.

5. DISCUSSION

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by significant heterogeneity in presentation, etiology, and treatment response. Recent research suggests that alterations in endogenous bioelectrical activity (EBA) play a crucial role in the pathogenesis of ASD, and these alterations may be amenable to modulation through non-invasive neuromodulation techniques such as REAC NPO and NPPOs.

EBA is a fundamental component of cellular and organismal physiology, influencing diverse processes such as wound healing, cell migration, and tissue regeneration. In the brain, EBA modulates neuronal activity, regulates synaptic plasticity, and influences the formation and maintenance of neural circuits and neurotransmission. Additionally, EBA plays a critical role in epigenetics, the study of heritable changes in gene expression that do not involve alterations to the underlying DNA sequence. One of the ways EBA affects gene expression is by influencing the methylation of DNA, a process that adds methyl groups to the DNA molecule, affecting its accessibility to transcription factors and thereby regulating gene expression.

Studies have shown that individuals with ASD exhibit altered brain connectivity, with abnormalities in synaptic transmission and plasticity. This suggests that EBA alterations may contribute to the development of ASD by affecting gene expression and neuronal connectivity.

REAC technology utilizes asymmetrically conveyed radioelectric fields to optimize EBA at different levels of organization. By considering the essential role of EBA in epigenetic processes, neuroplasticity, and neurotransmission, it is evident that REAC treatments aimed at optimizing EBA across multiple levels represent a promising technological approach to precision medicine, particularly in the context of ASD.

REAC NPO and NPPOs are non-invasive and painless neuromodulation treatments that have shown promising results in improving the symptoms of ASD. These treatments target the neurobiological and postural imbalances that are common in individuals with ASD, potentially leading to improvements in functional abilities.

In this study, REAC NPO and NPPOs were found to significantly improve functional abilities in children and adolescents with ASD across multiple domains assessed by the PEDI-CAT. These improvements were observed in the Activities of Daily Living, Mobility, Social Cognition, and Responsibility domains.

These findings suggest that REAC NPO and NPPOs have the potential to be effective treatments for enhancing the functional abilities of individuals with ASD. By optimizing individual EBA alterations, REAC technology may provide a novel and non-invasive approach to precision medicine for ASD.

Further research is needed to better understand the mechanisms of EBA alterations and the effects of REAC neuromodulation treatments on these mechanisms, particularly with respect to neurotransmission disorders and epigenetic dysregulation in ASD. However, the promising results presented in this study suggest that REAC NPO and NPPOs warrant further investigation as potential treatments for ASD.

6. CONLUSIONS

This doctoral research has delved into the application of the REAC technology neurobiological treatments for modulating epigenetic neurobiology, particularly focusing on Autism Spectrum Disorder (ASD).

This research has significantly contributed to the burgeoning field of REAC neurobiological modulation therapies, which hold promise in addressing a diverse range of neuropsychological disorders.

The REAC technology, with its ability to reinstate cellular polarity and rebalance the endogenous bioelectric field, represents a groundbreaking approach with paramount relevance in addressing neurological dysfunctions, particularly impacting neural communication mechanisms.

In the intricate landscape of ASD, characterized by challenges in communication, social interaction, and behavior, my research has sought to explore the potential of REAC technology in enhancing functional abilities. By actively contributing to the global understanding of how targeted treatments, such as REAC, can optimize endogenous bioelectrical activity, this research aligns with the broader initiative aimed at advancing knowledge and disseminating insights into the application of REAC neurobiological modulation therapies in precision medicine.

It is my fervent belief that these efforts will contribute to the evolving landscape of therapeutic interventions for individuals with neuropsychological disorders, offering hope for improved outcomes and quality of life.

Key Findings:

• Autism is a complex and diversified neurological and neuropsychiatric disorder influenced by a variety of genetic and epigenetic factors, presenting challenges in communication, social interaction, and behavior.

The bidirectional relationship between depression and ASD, the complex connection between anxiety and ASD, and the impact of internalization disorders on various conditions, including ASD, have been explored.

The intricate interplay between endogenous bioelectrical activity, epigenetics and neurodevelopment offers novel insights into neurodevelopmental disorders like ASD.

The REAC technology, with its unique design and low-intensity radio electric field, has shown promise in addressing neurological dysfunctions, impacting neural communication mechanisms, and restoring cellular polarity and harmonizing the endogenous bioelectric field.

The published research work carried out as part of doctoral program has demonstrated the effectiveness of REAC non-invasive neurobiological stimulation in mitigating the impact of internalizing disorders in ASD, alleviating stress impact, and improving functional abilities in children and adolescents with ASD.

The potential of REAC technology in neuromodulation therapies for various conditions, including ASD, depression, anxiety, and stress, as well as its effectiveness in restoring tissue and organ function and healing wounds, represents a significant advancement in the field. Ongoing research will continue to uncover the full potential of REAC technology.

This doctoral thesis has contributed to the growing understanding of the potential of REAC technology in addressing neuropsychological disorders, particularly in the context of ASD, and offers hope for improved therapeutic interventions and outcomes.

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