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The Non-Pharmaceutical Impact of MNRI on the levels of neurotransmitters associated with Inflammatory Processes

Tatiana V. Tatarinova [1-4], Trina Deiss [5], Lorri Franckle [6], Susan Beaven [7], Jeffrey Davis [8]

1 University of La Verne, La Verne, CA, USA

2 Vavilov Institute for General Genetics, Moscow, Russia

3 Siberian Federal University, Krasnoyarsk, Russia

4 Information Transmission Problems Institute, Moscow, Russia

5 United1Front Foundation, Minneapolis, MN, USA

6 Laser Health, Orlando, FL, USA

7 St. Petersburg Free Clinic, St. Petersburg, FL, USA
8 Prairie Health and Wellness, Wichita, KS, USA

* Correspondence: ttatarinova@laverne.edu

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Abstract: Neurotransmitter level of representatives from five different diagnosis groups were tested before and after participation in the MNRI® - Masgutova Neurosensorimotor Reflex Intervention. The intention was to ascertain neurological impact on 1) Developmental disorders, 2) Anxiety disorders/OCD (Obsessive Compulsive disorder), PTSD (Post-Traumatic Stress disorder)3) Palsy/Seizure disorders, 4) ADD/ADHD (Attention Deficit disorder/Attention Deficit Disorder Hyperactive Disorder), and 5) ASD (Autism Spectrum Disorder) disorders. Each participant had a form of neurological dysregulation and typical symptoms respective to their diagnosis. These diagnoses have severe negative impact on quality of life, immunity, stress coping, cognitive skills, and social assimilation. The resulting optimization and normalization of neurological and immunological functioning is substantiated by results thereby authenticating the MNRI method as an effective non-pharmacological neuromodulation treatment of neurological disorders. The effects of MNRI on inflammation has not yet been assessed. The resulting post-MNRI changes in participants' neurotransmitters show significant adjustments in the neurotransmitters regulation resulting in being calmer, a decrease of hypervigilance, increase in stress resilience, behavioral and emotional regulation improvements, more positive emotional state, and greater control of cognitive processes. We demonstrated that MNRI approach is an intervention that not only reduces inflammation, reduces oxidative stress, and encourages homeostasis of excitatory neurotransmitters. MNRI facilitates neurodevelopment, stress resiliency, neuroplasticity, and optimal learning opportunity. There have been no reported side effects of MNRI treatments.

Keywords: neurotransmitters; inflammation; MNRI

1. Introduction

Normal regulation and balance of the neurotransmitters is important to the homeostasis of the body, since chronic neurodegenerative diseases often have mitochondrial and neuroinflammation dysfunctions. Inflammation processes are manifested in many diseases and disorders such as cerebral palsy, epilepsy, autism, post-traumatic stress disorder (PTSD), as well as autoimmune diseases [1, 2, 3]. The elevation of

cortisol in these conditions becomes the driving factor for increased levels of phenylethanolamine N-methyltransferase (PMNT). This effect is demonstrated by a reduction in epinephrine levels prior to a change in norepinephrine thus leading to oxidative stress and/or inflammation [4, 5]. Another key enzyme is monoamine oxidase A (MAO), mediating the turnover of noradrenaline. MAOs are important in the breakdown of monoamines ingested in food and serve to inactivate monoamine neurotransmitters. MAO is correlated with neurotransmitter excitation and elevated levels of MAO are found in the same disorders as PMNT. MAO assists with degradation of aspects of the serotonergic, adrenergic and dopaminergic systems, therefore MAO dysfunction has been detected in ADHD and ASD cases. The third factor is N-methyl-D-aspartate receptor (NMDA), which is a glutamate receptor (Figure 1). Excitotoxicity caused by overactivation of this receptor has been connected to many neurogenerative disorders, especially epilepsy [6, 7, 8, 9].

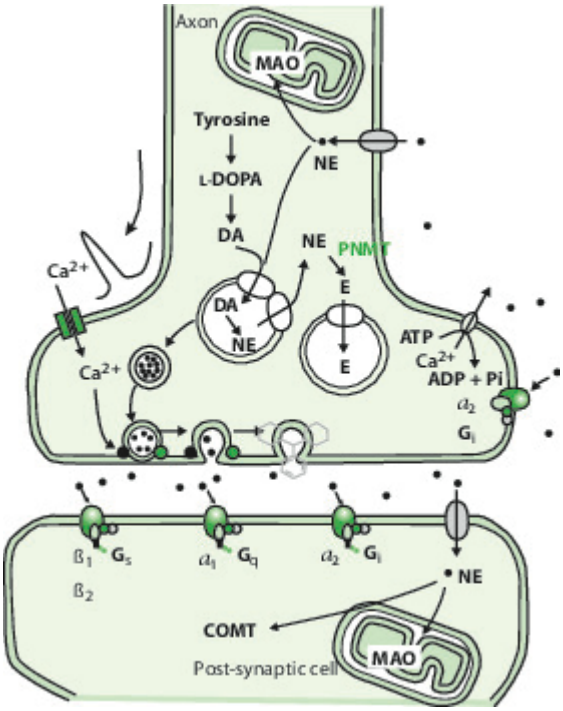

Figure 1. Demonstration of the biosynthesis of adrenaline involving a series of enzymatic reactions (Source: own, SMEI [Svetlana Masgutova Educational Institute], LLC).

It has been found that adrenergic hormones, such as adrenaline, can produce retrograde enhancement of long-term memory in humans. The release of adrenaline due to emotionally stressful events, which is endogenous adrenaline, can modulate memory consolidation of the events, ensuring memory strength that is proportional to memory importance.

When dysfunction of these enzymes and receptors occurs, then symptomatic issues become more pronounced and create a chronic inflammation, thus driving diseases and disorders further into pathology [10]. In our study, the MNRI approach trended towards normalization of PMNT, MAO and NMDA functions effectively and non-pharmaceutically without adverse effects, thereby mitigating disease processes.

The intent of this study is to determine the effectiveness of the MNRI therapy for disorders such as 1) developmental disorders 2) anxiety disorders 3) palsy/seizure disorders 4) ADD/ADHD, and 5) ASD disorders utilizing analysis of neurotransmitter markers. The assessment of neurotransmitters via urinalysis is both the least invasive and most optimal way to measure these biomarkers, since venipuncture and cerebral spinal fluid collection methods have various complications [73-75]. Importantly, the CSF neurotransmitter optimal ranges have yet to be established.

Utilization of urine using Fluorometric methods and High-Performance Liquid Chromatography (HPLC) methodology have expanded parameters to greater specificity and sensitivity, allowing an even wider span of clinical applications [11]. There are several advantages of using this approach:

A. Reliability and quality assurance are established with the use of CLIA certified labs.

B. Since the 1960s, several studies depended upon biomarkers of neurotransmitters and metabolites [11].

C. Several studies concluded that there is direct correlation between urine and CNS neurotransmitters [13, 14, 15]. Many researchers and clinicians are formally using urinary neurotransmitters as biomarkers, and as a diagnostic and assessment tool [12, 16, 14, 15].

2. Results

The following neurotransmitters were evaluated in this paper: (1) epinephrine, (2) norepinephrine, (3) dopamine, (4) serotonin, (5) glutamate, (6) glycine, (7) histamine, (8) DOPAC, and (9) 5HIAA. These chemical transmitters function throughout the whole human organism and communicate by targeting specific cells. The immune and central nervous systems are interconnected and co-responsive with each other. A complex modulatory system exists between the central nervous (CNS) and immune systems. A body is hardwired to have a "cause-and-effect" relationship between the sympathetic (SNS) and parasympathetic (PNS) nervous systems. Neuroendocrine hormones regulate cytokine balance; the immune system works simultaneously for inhibition and excitation processes. These systems allow for ongoing adaptations on a cellular, psychological, immunological, and structural level. Oxidative stress can facilitate infraction of homeostasis between immune and nervous systems [17, 18, 19, 20, 21].

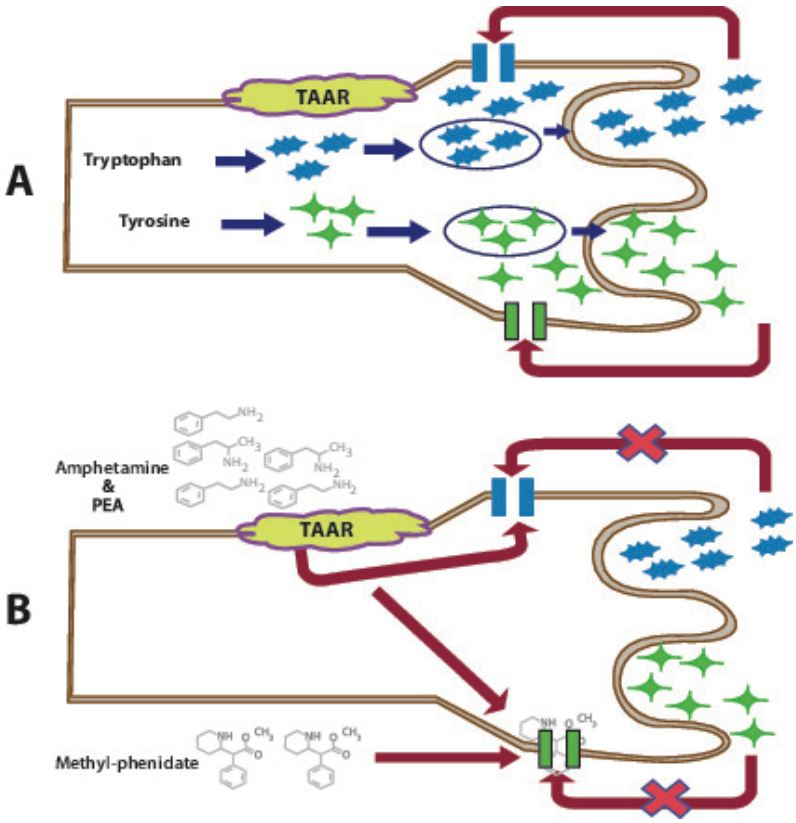

Figure 2. Schematic of the inhibition of the dopamine and serotonin transporters by PEA, amphetamine, and methylphenidate. Panel A shows the normal action of release and re-uptake of the biogenic amines, dopamine and serotonin. Panel B shows the modulation of the monoamine re-uptake transporters by PEA and amphetamine through TAAR, as well as the blockage of the dopamine transporter by methylphenidate. (Source: own, SMEI [Svetlana Masgutova Educational Institute], LLC).

Norepinephrine and epinephrine both affect alpha and beta receptors. These are part of the fight-and-flight responses that are initiated under stress. Norepinephrine is a precursor to epinephrine. The first response is norepinephrine through the sympathetic nervous system. Activation of norepinephrine raises alertness, preparing the body for an action, increases heart rate, blood pressure, and glucose storage and facilitating blood flow to skeletal muscles. If the stress continues or increases, norepinephrine is converted to epinephrine [22, 23, 24, 14].

Norepinephrine can be activated by both pre- and post-synaptic adrenergic receptors, thereby it can be either released in the locus coeruleus, where it is beneficial for long-term memory as a neurotransmitter, or in the adrenal medulla, where it functions as a hormone.

Dopamine as also is a hormone as well as a neurotransmitter. Dopamine is a precursor in the synthesis of the neurotransmitters norepinephrine and epinephrine. There are two common functions of dopamine: (1) in association to the motivational construct of reward-motivational behavior, and (2) in motor control. Dopamine function is directly associated with the kidneys, pancreas, intestinal mucosa, digestion and gastrointestinal motility (Figure 2) [25, 26, 13].

Glycine works as an immunomodulator, a cytoprotective agent and an anti-inflammatory regulator. The overall health of a person directly depends on the functioning of glycine. Whether it is produced in the liver for detoxification, or it is facilitating synthesis of bile and amino acids, it plays a role in suppression of activation of transcription factors and formation of free radicals and cytokines. Glycine also participates in building DNA and RNA molecules. Excessive amounts of glycine can lead to decreased energy, anxiousness, sleep difficulties, as well as immune dysregulation and digestive stress [27].

Histamine, which is well-known for its inflammatory response, is also involved in regulation of the overall physiological responses of the gut and local immune response (Figure 3). The posterior hypothalamus houses the tuberomammillary nucleus (TMN), where the histamine neurons are responsible for the arousal portion of the sleep-wake cycle. This is the location, where quick firing production is utilized for wakefulness and then is slowed progressing towards rest or sleep and is completely stopped during the REM sleep stage [28].

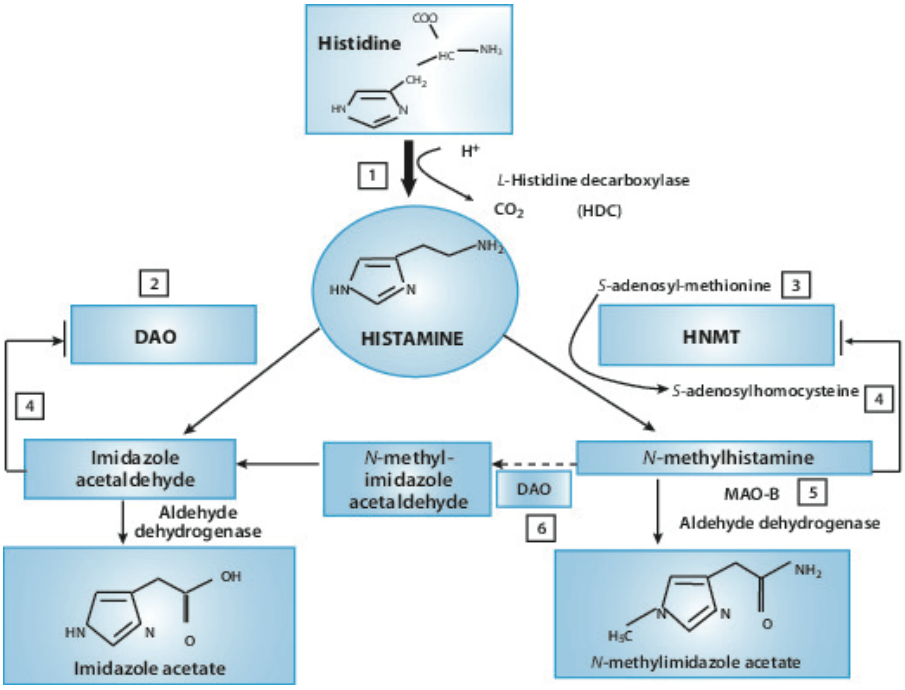

Figure 3. Summary of the histamine metabolism. The biogenic amine histamine is synthesized by decarboxylation of the amino acid histidine catalyzed by L-histidine decarboxylase (HDC) (1). Histamine can be metabolized by extracellular oxidative deamination of the primary amino group by diamine oxidase (DAO) (2) or intracellular methylation of the imidazole ring by histamine-N-methyltransferase (HNMT) (3). Therefore, insufficient enzyme activity caused by enzyme deficiency or inhibition may lead to accumulation of histamine. Both enzymes can be inhibited by their respective reaction products in a negative feedbackloop (4). N-Methylhistamine is oxidatively deaminated to N-methyl-imidazole acetaldehyde by monoamine oxidase B (MAO B) (5) or by DAO (6). Because the methylation pathway takes place in the cytosolic compartment of cells, MAO B (5) has been suggested to catalyze this reaction in vivo (35) [29].

DOPAC is a metabolite of dopamine. Dysfunction of dopamine leads to various nervous system disease or disorders. If the origination of dysfunction is oxidative stress, it will have a direct impact on health. MAO, associated with oxidative stress, is the enzyme that breaks down dopamine to DOPAC [26, 30].

Our results (Tables 1-5) show that MNRI 8-day intensive treatment experience causes considerable changes in neurotransmitter activity of the patients. Neurotransmitters are intricately involved in homeostasis; they are crucial to modulating behaviors and functioning of the immune system. These chemical messages are

transmitted by neural synapses specific to each transmitter; a neurotransmitter is released by a presynaptic neuron and then acts on a postsynaptic target cell, and every neurotransmitter has multiple receptor molecule types. Neurotransmitters are differentiated by their mechanism of action regarding action potential: they can be either excitatory or inhibitory. Inhibitory will prevent action potential whereas excitatory will enhance action potential. Several studies suggested [31, 32, 33]. that neurotransmitters have respective and collaborative involvement in cognitive processes, including memory. In one study [33] it was determined that the greatest impact of neurochemical imbalance was that of spontaneous decision making.

Several studies were supportive of the existence of intricate communication between the immune system and the nervous system [34]. It has been demonstrated, that in addition to neurotransmitters signaling through lymphocyte cell-surface receptors initiating modulation, leukocytes can release neurotransmitters achieving autocrine and paracrine modulation [3].

3. Discussion

We limit our consideration to neurotransmitters with p-values < 0.05. Comparisons include control (Ct) vs pre-treatment (Pr), control vs post-treatment (Ps) and pre vs post-treatment. Below we discuss our finding for different groups of patients.

3. 1 Developmental Disorders

Developmental Disorders (n=34)		Epine-phrine (ug/g Cr)	Norepine-phrine (ug/g Cr)	Glutamate (umol/g Cr)	Glycine (umol/g Cr)	bPEA (nmol/g Cr)	Histamine (ug/g Cr)	GABA (umol/g Cr)	DOPAC (umol/g Cr)	5-HIAA (ug/g Cr)
Controls	Mean (μ)	1.80	31.8	21.5	1004.8	40.7	24.7	4.21	468.9	2460.1
	SD	0.75	13.6	10.1	552.1	19.1	9.7	1.15	131.1	1434.8
Pre-Tx	Mean (μ)	4.64	62.3	70.9	1536.2	57.4	44.1	9.40	997.7	6271.0
	SD	2.91	27.7	49.9	558.7	18.3	20.1	3.43	744.7	3274.9
Post-Tx	Mean (μ)	3.46	62.2	65.7	1398.6	51.7	41.9	8.95	1003.5	6181.5
	SD	1.76	29.2	43.5	600.9	22.4	23.0	3.41	491.6	2788.6
Difference (%)	Controls vs. PreTx	158%	96%	229%	53%	41%	79%	123%	113%	155%
	Controls vs. PostTx	92%	95%	205%	39%	27%	70%	113%	114%	151%
	PreTx vs. PostTx	-25%	0%	-7%	-9%	-10%	-5%	-5%	1%	-1%
Statistical Significance	Controls vs. PreTx	***	***	***	**	**	***	***	***	***
	Controls vs. PostTx	***	***	***	*	T	***	***	***	***
	PreTx vs. PostTx	*	ns	ns	ns	ns	ns	ns	T	ns
Effect Size	Controls vs. PreTx	VL	VL	VL	Lg	Lg	VL	VL	Lg	VL
	Controls vs. PostTx	VL	VL	VL	Md	Md	Lg	VL	VL	VL
	PreTx vs. PostTx	Sm	NoEf	NoEf	Sm	Sm	NoEf	NoEf	NoEf	NoEf

Table 1. Study Group 1. Developmental disorders (n=34). Comparisons between levels of epinephrine, norepinephrine, dopamine, serotonin, glutamate, glycine, histamine, DOPAC, 5=HIAA for control (Ct), pre-treatment (Pr), and post-treatment (Ps). Asterixis '*', '**', and '***' denote three levels of significance corresponding to P-value < 0.05, < 0.01, and < 0.001, respectively.

There is a relationship between levels of epinephrine and norepinephrine. Norepinephrine is continually released into the bloodstream; while epinephrine is synthesized from norepinephrine only under stress. In the "developmental disorders" study group we found a significant reduction in epinephrine (p-value < 0.05, medium effect of -0.5), but no change in the norepinephrine level. Because there is no change in norepinephrine, we speculate that enzyme phenylethanolamine N-methyltransferase (responsible for conversion of norepinephrine to epinephrine) is operating at a reduced capacity, suggesting reduction in cortisol levels. Consequently, less inflammatory stress will result in diminished anxiety, better coping mechanism, and ability to reach higher cognitive functioning. Implications of chronic stress levels leading to inflammation (existence of stress-related diseases) was demonstrated in many studies. A chronic increase of allostasis will lead to pathophysiology [3]. A study conducted at the Uppsala University demonstrated that the more serotonin their subjects produced, the more anxious they became [35]. When there is a reduction in serotonin yet no change in 5HIAA, its byproduct, there is often a parallel decline in anxiety. Interestingly, in this study group (even though glycine levels showed no statistical change) there was a small effect of -0.2, suggesting decreased inflammation and, possibly, improved sleep and reduced anxiety. Glycine levels were still above the levels in the healthy control group but shifted closer to the normal range. Note, that high levels of glycine are indicative of potential neurological disorders. When more than 0.5g/kg of glycine is absorbed, adverse central nervous reactions occur in children [69]. An excessive amount of glycine will result in anxiousness, sleep disturbances, and immune and digestive dysregulation. On the other hand, glycine is a well-known cytoprotective agent playing a role in immunomodulation. It acts on inflammatory cells such as macrophages to suppress activation of transcription factors and the formation of free radicals and inflammatory cytokines [36].

3.2 Anxiety/OCD (Obsessive Compulsive disorder) /PTSD (Post-Traumatic Stress disorder)

Anxiety/OCD/ PTSD (n=20)		Epinephrine (ug/g Cr)	Norepinephrine (ug/g Cr)	Glutamate (umol/g Cr)	Glycine (umol/g Cr)	bPEA (nmol/g Cr)	Histamine (ug/g Cr)	GABA (umol/g Cr)	DOPAC (umol/g Cr)	5-HIAA (ug/g Cr)
Controls	Mean (μ)	1.80	31.8	21.5	1004.8	40.7	24.7	4.21	468.9	2460.1
	SD	0.75	13.6	10.1	552.1	19.1	9.7	1.15	131.1	1434.8
Pre-Tx	Mean (μ)	3.05	50.5	65.3	1474.3	62.2	42.4	9.32	714.8	6385.2
	SD	1.41	20.5	42.8	404.6	33.1	21.4	4.01	233.6	3368.1
Post-Tx	Mean (μ)	2.98	50.3	53.2	1367.1	55.8	41.0	8.40	796.5	6195.0
	SD	1.29	27.5	30.3	442.9	26.0	21.0	3.63	242.2	2886.2
Difference (%)	Controls vs. PreTx	70%	59%	203%	47%	53%	72%	121%	52%	160%
	Controls vs. PostTx	66%	58%	147%	36%	37%	66%	99%	70%	152%
	PreTx vs. PostTx	-2%	0%	-19%	-7%	-10%	-3%	-10%	11%	-3%
	Controls vs. PreTx	***	***	***	*	*	***	***	***	***

Statistical Significance	**Controls vs. PostTx**	***	**	***	T	*	***	***	***	***
	PreTx vs. PostTx	ns	ns	ns	ns	ns	ns	ns	ns	ns
Effect Size	**Controls vs. PreTx**	Lg	Lg	VL	Lg	Md	Lg	VL	VL	VL
	Controls vs. PostTx	Lg	Lg	VL	Md	Md	Lg	VL	VL	VL
	PreTx vs. PostTx	NoEf	NoEf	Sm	Sm	Sm	NoEf	Sm	Sm	NoEf

Table 2. Study Group 2. Anxiety/OCD disorders (n=20). Comparisons between levels of epinephrine, norepinephrine, dopamine, serotonin, glutamate, glycine, histamine, DOPAC, 5=HIAA for control (Ct), pre-treatment (Pr), and post-treatment (Ps). Asterixis '*', '**', and '***' denote three levels of significance corresponding to P-value < 0.05, < 0.01, and < 0.001, respectively.

There were several trends observed in this study group (Table 2). First, there was a reduction in glutamate and glycine (small effects of -0.3 and -0.2 respectively). Glutamate has excitatory and glycine has inflammatory effect. Since there is a decrease of GABA levels (-0.2) and in glutamate levels, we propose that the reduction of GABA occurs due to the reduction of glutamate. In addition to the inhibitory effects of GABA on the CNS, there are also receptor transcripts evident in immune cells. GABA is also believed to work with t-cells. [37].

As discussed above, MAO activity appears to be enhanced post MNRI treatments, this claim is supported by increase in DOPAC and no change in dopamine, norepinephrine or epinephrine levels. Symptomatic characterizations of this study group are anxiety, depression, sleep disturbances, immunity issues, rage, headaches, heart palpations, and panic attacks. All these symptoms make a body susceptible to immune disorders. New studies in neuropsychopharmacological have demonstrated connections between immune disorders and neuropsychiatric diseases [38]. Interruptions in the inflammation excitatory process will translate into less symptomatic responses and better ability to enjoy life and having adaptive coping skills.

Subjective statements from the participants report they feel more relaxed, or they have less repetitive or negative thoughts.

3.3 Palsy and Seizures

Interestingly, this study group showed several notable changes indicative of reduction of inflammatory or oxidative stress (Table 3). Levels of four neurotransmitters (epinephrine, norepinephrine, glycine, and GABA) demonstrated significant changes. Palsy and seizure patients can complain about ataxia, rigidity, athetosis, eating disorders, spasticity or hypo/hyperactive muscle control [39] Epidemiology of seizure disorders are not fully understood; however, a generally accepted definition is that of a heterogeneous compilation of various syndromes or neurological conditions that present with recurrent, unprovoked, paroxysmal seizures [40].

Palsy & Seizures (n=16)		**Epinephrine (ug/g Cr)**		**Norepinephrine (ug/g Cr)**	**Glutamate (umol/g Cr)**	**Glycine (umol/g Cr)**	**bPEA (nmol/g Cr)**	**Histamine (ug/g Cr)**	**GABA (umol/g Cr)**	**DOPAC (umol/g Cr)**	**5-HIAA (ug/g Cr)**
Controls	**Mean (μ)**	1.80	31.8	21.5	1004.8	40.7	24.7	4.21	468.9	2460.1	
	SD	0.75	13.6	10.1	552.1	19.1	9.7	1.15	131.1	1434.8	
Pre-Tx	**Mean (μ)**	4.21	59.0	101.9	3136.9	76.2	52.9	15.01	921.9	10119.4	
	SD	2.61	20.6	49.2	1681.4	36.2	20.7	7.29	544.5	5422.2	
Post-Tx	**Mean (μ)**	3.45	66.6	103.9	2734.5	80.5	52.8	13.48	878.0	10331.0	

PostTx	SD	1.70	24.7	41.8	1312.0	39.3	25.8	6.96	379.7	6384.1
Difference (%)	Controls vs. PreTx	134%	85%	373%	212%	87%	114%	257%	97%	311%
	Controls vs. PostTx	92%	109%	382%	172%	98%	114%	220%	87%	320%
	PreTx vs. PostTx	-18%	13%	2%	-13%	6%	0%	-10%	-5%	2%
Statistical Significance	Controls vs. PreTx	***	***	***	***	***	***	***	***	***
	Controls vs. PostTx	***	***	***	***	***	***	***	***	***
	PreTx vs. PostTx	ns	ns	ns	ns	ns	ns	ns	ns	ns
Effect Size	Controls vs. PreTx	VL	VL	Hg	VL	VL	VL	Hg	Lg	VL
	Controls vs. PostTx	VL	VL	Hg	VL	VL	VL	VL	VL	VL
	PreTx vs. PostTx	Sm	Sm	NoEf	Sm	NoEf	NoEf	Sm	NoEf	NoEf

Table 3. Study Group 3. Palsy & Seizures disorders (n=16). Comparisons between levels of epinephrine, norepinephrine, dopamine, serotonin, glutamate, glycine, histamine, DOPAC, 5=HIAA for control (Ct), pre-treatment (Pr), and post-treatment (Ps). Asterixis '*', '**', and '***' denote three levels of significance corresponding to P-value $< 0.05, < 0.01$, and < 0.001, respectively.

Level of glycine showed a small reduction (-.03), meaning that while the numbers were above the control range, they progressed nearer post treatment. Glycine is a marker for inflammation. While proper functioning glycine is a protective agent, its excess has been found to exasperate symptoms of palsy and seizures. Nonketonic hyperglycinemia (NKH) is one example of this. NKH presents within the first week of birth with low muscle tone, need for ventilation, weakness, and possible seizures. This progresses into abnormal jerking movements and hypotonia of all systems [70]. Glycine is present in both the brainstem and spinal cord and forebrain. Functions are related to various motor and sensory functions, in the forebrain studies have concluded that the N-methyl-D-aspartate (NMDA) receptor-gated ion channel is regulated by glycine [41]. NMDA is a glutamate receptor, modifying the action of glycine [42], so glycine can switch between being excitatory and inhibitory.

Our study demonstrated reduction in epinephrine (small effect -0.3) and an elevation in norepinephrine (small effect 0.3). These observations combined with no change in dopamine imply that the MNRI treatment did not change dopamine levels, acting directly on norepinephrine and epinephrine. Because epinephrine levels decrease, and epinephrine levels increase without dopamine involvement, this may indicate involvement of cortisol or PMNT, leading to reduction in oxidative or inflammatory stress.

Respiratory system can also be impacted by the reduction glycine and GABA (significantly reduced with p-value<0.05, medium effect -0.2). GABA inhibits the CNS; several studies found increased tonic inhibition related to extrasynaptic GABA-A receptors in traumatic brain injuries or strokes, contributing to subsequent functional impairment [43]. High levels of GABA can have adverse effects on patients, such as gastric distress, constipation, fatigue, breathing difficulties, muscle weakness, and reduced appetite.

3.4 Attention Deficit Disorder/Attention Deficit Disorder Hyperactive Disorder (ADD/ADHD)

These disorders demonstrate a consistent pattern of both impulsivity and inattention. Cytokines have an intricate role in tryptophan metabolism and dopaminergic pathways, therefore alteration in levels of anti-inflammatory and pro-inflammatory cytokines may have influence on the pathogenesis of ADHD [43, 44]. Individuals who suffer from ADD or ADHD are known to have highly efficient and greater number of dopamine reuptake inhibitors. If dopamine is removed too quickly it is no longer able to fulfil its role. Table 4 shows results for the control and treatment groups. Therefore, stimulants are utilized in order to block dopamine transporters thus allowing dopamine more time to impact cells. There is a small (-0.3 effect, p-

value<0.05) reduction of dopamine and an elevated DOPAC (p-value <0.01, medium effect of 0.6), suggesting that there is increase in the MAO activity. We conclude that MNRI treatment is impacting MAO activity in its participants with a medium effect.

ADD/ADHD (n=24)		Epinephrine (ug/g Cr)	Norepinephrine (ug/g Cr)	Glutamate (umol/g Cr)	Glycine (umol/g Cr)	bPEA (nmol/g Cr)	Histamine (ug/g Cr)	GABA (umol/g Cr)	DOPAC (umol/g Cr)	5-HIAA (ug/g Cr)
Controls	Mean (μ)	1.80	31.8	21.5	1004.8	40.7	24.7	4.21	468.9	2460.1
	SD	0.75	13.6	10.1	552.1	19.1	9.7	1.15	131.1	1434.8
Pre-Tx	Mean (μ)	3.04	60.6	74.6	1541.7	68.7	49.5	8.88	678.1	5527.5
	SD	1.47	28.4	50.2	582.0	32.9	22.5	3.53	211.5	2569.4
Post-Tx	Mean (μ)	2.87	57.7	55.3	1332.4	54.6	39.3	7.71	845.0	5327.7
	SD	1.28	30.8	33.4	433.0	25.0	19.6	3.12	307.6	2020.1
Difference (%)	Controls vs. PreTx	69%	90%	246%	53%	69%	101%	111%	45%	125%
	Controls vs. PostTx	59%	81%	157%	33%	34%	59%	83%	80%	117%
	PreTx vs. PostTx	-6%	-5%	-26%	-14%	-21%	-21%	-13%	25%	-4%
Statistical Significance	Controls vs. PreTx	***	***	***	**	***	***	***	***	***
	Controls vs. PostTx	***	***	***	T	*	***	***	***	***
	PreTx vs. PostTx	ns	ns	*	ns	*	*	T	**	ns
Effect Size	Controls vs. PreTx	Lg	VL	VL	Lg	Lg	VL	VL	Lg	VL
	Controls vs. PostTx	Lg	Lg	VL	Md	Md	Lg	VL	VL	VL
	PreTx vs. PostTx	NoEf	NoEf	Sm	Sm	Sm	Sm	Sm	Md	NoEf

Table 4. Study Group 4. ADD/ADHD disorders (n=24). Comparisons between levels of epinephrine, norepinephrine, dopamine, serotonin, glutamate, glycine, histamine, DOPAC, 5=HIAA for control (Ct), pre-treatment (Pr), and post-treatment (Ps). Asterixis '*', '**', and '***' denote three levels of significance corresponding to P-value < 0.05, < 0.01, and < 0.001, respectively.

Microglia are the main resident immune cells of the brain. When activated, microglial cells release pro-inflammatory cytokines and other factors such as glutamate, contributing to neuroinflammation. A crosstalk between peripheral immune cells and microglia can potentiate inflammation both in the periphery and in the brain. Post MNRE levels of glutamate and histamine are found to be reduced in our study (Glutamate is lowered by -0.4, pvalue<0.05, histamine at p-value<0.05, effect -0.5). Recall that glutamate, glycine, and histamine are inflammatory markers, and the histamine is a substrate of MAO. Therefore, we demonstrated that MNRI not only reduces the inflammation but also modulates MAO activity in the body.

3.5 Autism Spectrum Disorders

Patients with ASD frequently report high levels of oxidative stress and/or extremes of hyper- or hypo-arousal. We have observed (Table 5) no change in dopamine or epinephrine levels, however, a reduction in norepinephrine at p-value <0.01 and small effect of -0.4. This suggests that norepinephrine is being metabolized by monoamine oxidases (MAO), because norepinephrine is a substrate target for MAO. Both too much and too little of MAO negatively affects its function. This imbalance is associated with depression, attention deficit, addictions, migraines, and irregular sexual maturation. Serotonin is another MOA target, which is reduced as a result of the treatment (p <0.05 with a small effect of -0.3). MAO is responsible for metabolizing serotonin to 5HIAA. Prior studies conclude that there is an impairment in the proper functioning of MAO in subjects with Autism and ASD sub-diagnosed [45]. Decreased activity of MAOs may lead to increased levels of monoaminergic neurotransmitters, such as serotonin, which have been suggested to have a critical role in autism [46]. Therefore, we suggest that MNRI activates modulation of MAO activity. This is supported by reports of caregivers stating that the participants have less anxiety, they sleep better, and can recognize social cues. Even though palmitoylethanolamide (PEA) is sometimes utilized to treat ASD patients,

its excess it is associated with "mind racing", sleep disturbances, anxiety, irritability, and even schizophrenia [47]. The downstream binding of PEA to the trace amine-associated receptor (TAAR1) results in monoamine functioning, thereby potentially inhibiting the re-uptake of dopamine, serotonin, and norepinephrine. If this process continues, there is an increased concentration of PEA at the synapse [25]. There is also a possibility that phenylethanolamine N-mehtyltransferase, the same enzyme that metabolizes epinephrine to norepinephrine, also metabolizes PEA. Since 5HIAA does not increase with the reduction of serotonin, it is possible that serotonin may be maintaining melatonin levels. This hypothesis is again supported by subjective statements from participants that reported improved sleep and enhanced mood.

Autism Spectrum Disorder (n=22)		Epinephrine (ug/g Cr)	Norepine-phrine (ug/g Cr)	Glutamate (umol/g Cr)	Glycine (umol/g Cr)	bPEA (nmol/g Cr)	Histamine (ug/g Cr)	GABA (umol/g Cr)	DOPAC (umol/g Cr)	5-HIAA (ug/g Cr)
Controls	Mean (µ)	1.80	31.8	21.5	1004.8	40.7	24.7	4.21	468.9	2460.1
	SD	0.75	13.6	10.1	552.1	19.1	9.7	1.15	131.1	1434.8
Pre-Tx	Mean (µ)	6.64	55.6	55.5	1640.1	71.7	55.5	9.13	730.5	7142.1
	SD	6.08	26.4	34.2	585.4	34.1	32.3	3.03	339.7	3173.6
Post-Tx	Mean (µ)	6.57	46.2	54.7	1584.6	60.6	48.4	7.69	750.6	7240.0
	SD	6.20	24.0	35.8	741.9	35.1	32.4	2.29	296.7	2763.0
Difference (%)	Controls vs. PreTx	269%	75%	158%	63%	76%	125%	117%	56%	190%
	Controls vs. PostTx	265%	45%	154%	58%	49%	96%	83%	60%	194%
	PreTx vs. PostTx	-1%	-17%	-2%	-3%	-16%	-13%	-16%	3%	1%
Statistical Significance	Controls vs. PreTx	***	***	***	***	***	***	***	***	***
	Controls vs. PostTx	***	**	***	**	**	***	***	***	***
	PreTx vs. PostTx	ns	*	ns	ns	T	ns	*	ns	ns
Effect Size	Controls vs. PreTx	Lg	Lg	VL	Lg	Lg	VL	Hg	Lg	VL
	Controls vs. PostTx	Lg	Md	VL	Lg	Md	Lg	VL	VL	Hg
	PreTx vs. PostTx	NoEf	Sm	NoEf	NoEf	Sm	Sm	Md	NoEf	NoEf

Table 5. Study Group 5. Autism spectrum disorders (n=22). Comparisons between levels of epinephrine, norepinephrine, dopamine, serotonin, glutamate, glycine, histamine, DOPAC, 5=HIAA for control (Ct), pre-treatment (Pr), and post-treatment (Ps). Asterixis '*', '**', and '***' denote three levels of significance corresponding to P-value < 0.05, < 0.01, and < 0.001, respectively.

4. Materials and Methods

4.1 MNRI method

The MNRI method was originally developed in Russia in 1989, and further developed in Eastern Europe over the subsequent years. Several scientific studies and clinical observations have shown that this non-pharmacological treatment modality was significant positive results towards improvement in the neurological functioning in individuals with sensorimotor or reflex development deficits, behavior disorders, speech and

language pathologies, and learning disabilities [48, 49, 50, 51, 52, 53, 54]. MNRI appeared in the USA in 1996 and has gradually been accepted by professionals in over 40 countries. MNRI is called a neuromodulation method as it facilitates the neurodevelopment in individuals with various neurological deficits and enables them to improve their reflex circuit functions – integration of their sensory and motor aspects, postural control, motor coordination, and physiological markers [51, 52]. This neuroplasticity and skill development enable improved functioning, development, and learning [15, 49, 50, 51, 52, 53, 54]. The MNRI therapy program is based on the theory that impaired reflex circuits can be reconstructed and re-integrated, which involves awakening the genetic sensorimotor memory in individuals even with severe diagnosis (such as CP and brain damage) [51, 52]. MNRI is an evidence and research based therapeutic program which utilizes neuroplasticity via reflex integration techniques for the neurosensorimotor-cognitive development of children and adults with neurodeficits and learning problems [55]. Over the past 30 years, numerous studies have been conducted and articles published by Dr. S. Masgutova and her scientific colleagues from various international institutions [55].

MNRI is based on exercises and techniques called "repatterning" which essentially means re-educating, recoding, rerouting, and paving the reflex nerve pathways specific for dynamic and postural reflex schemes (e.g., Babinski, Automatic Gait, Bauer Crawling, Hands Grasp, and others) [55]. The stimulation of reflex pathways is aimed at strengthening and stabilizing the traces of genetic sensory-motor memory and at activation of the innate defense mechanisms through the body's neuroendocrinehormonal 'alarm' system (HPA axis) (hypothalamus-pituitary-adrenal gland stress response cycle activation) in times of stress or danger [17]. MNRI exercises stimulate innate neuro-regulatory mechanisms and enhance stress resiliency immune function [54, 48, 49]. Repatterning activates the extra pyramidal nervous system (peripheral nerves, spinal cord, brain stem, and diencephalon), which is responsible for targeting lower motor neurons in the spinal cord that are involved in reflexes, locomotion, complex movements, and postural control [56]. Repatterning also extends axonal linkage between neurons, facilitates the growth of neural nets, increases myelination, and facilitates new neural route pathways., as described by Sechenov [57, 58] Pavlov [59], Anokhin [60], Haines [18], Virella [19].

MNRI method addresses the neuro-sensorimotor aspect of early sensory-motor patterns and reflexes to support sensory-motor integration and neurodevelopment in children and adults with neurodeficits and learning challenges: CP, TBI [51, 52, 53, 54], ASD [49] Down syndrome [49, 50, 61, 62], and other neurological disorders [63, 71]. MNRI method meets the ever-increasing demands for neurorehabilitation of individuals with impaired sensorimotor functions due to central nervous system damage or dysfunction. Previous studies of the MNRI method and its different sub-programs demonstrated a positive effect on immune markers [64, 65, 50], neurophysiological functions [52, 53], and various developmental aspects including the regulation of behavior and emotions, language, and communication [66, 49, 67, 63].

4.2. Clinical Study Population

This study utilized a control group (n=50) to provide a comparative analysis of neurotransmitters. The participants who provided samples for the neurotransmitter tests were cleared of all inflammatory diseases or disorders or allergies. The control group exclusion criteria included the following diagnosis: attention-deficit/hyperactivity disorder, anxiety, autism and Asperger's syndrome, Alzheimer's disease, chronic migraines, depression, insomnia, obsessive compulsive disorder, Parkinson's disease, Cerebral Palsy, or PTSD. None of the individuals in the control group were taking medications or supplements at the time of sample submission. Only subjects aged 18 through 64 years were included, and a body mass index was calculated for all subjects. Only subjects with BMI in the normal range normal (18.5–24.9), as defined by the U.S. Department of Health & Human Services, were included in the control group.

The study group (n=116) contained participants who attended the MNRI conferences and signed the consent form, according to NEIRB regulations, did not add new supplements, medications, or participate simultaneously in other treatments, such as but not limited to Neurofeedback, CBD, or Cranial Sacral therapies. All participants were officially diagnosed and then categorized into five diagnosis groups. No participant was compensated in any way during this study. All samples were submitted according to the reference laboratory's protocol. Any samples omitted were done by the reference laboratory due to non-

conformity of the sample to the acceptance criteria. Some samples were not used because they did not meet reference standards, i.e. they were either too diluted, or missed either post- or pre-sample.

4.2.1 Description of Study Groups

Study group 1: Developmental Disorders (n=34) including Developmental Delay, Dyslexia, Heat defects, restricted growth and development, Down syndrome, and general developmental delay.

Study group 2: Anxiety Disorders, OCD, PTSD (n=20): subjects diagnosed, as per DSM-5 criteria, with disorders associated with anxiety, such as anxiety, obsessive compulsive disorder, and post-traumatic stress disorder. Subjects with major depressive mood disorder were not a part of this group.

Study group 3: Palsy and Seizures (n=16) diagnosis included one or more neurological disorders such as cerebral palsy, seizures, or Tourettes.

Study group 4: ADD/ADHD (n=24) all had official diagnosis of attention deficit disorder or attention deficit/ hyperactivity disorder.

Study group 5: ASD (n=22) inclusion of all diagnoses that fall within the Autism Spectrum Disorder according to The Diagnostic and Statistical Manual of Mental Disorders (DSM-5, published in 2013).

4.3 Laboratory Methods: Analysis of Urinary Catecholamine's and neurotransmitters

The urine test panel included nine neurotransmitters: epinephrine, norepinephrine, dopamine,4-dihydroxyphenylacetic acid (DOPAC), serotonin, 5-HIAA, glycine, glutamate, and histamine. The tested subjects were instructed to fast eight hours prior to going to bed but could drink plain water and take supplements or medications per doctors' orders and/or according to their six-month routine. On the morning of urine collection, the subjects were required to fast and avoid drinking any liquid. The first morning urine was voided and, two hours later, the second morning urine was collected for analysis. All urinary samples were stored frozen at −20°C and assayed within one week of collection. Urinary catecholamines and neurotransmitters were measured by competitive ELISA test. These IVD methods were CLIA approved and processed by a CLIA licensed reference laboratory (Pharmasan Labs, Osceola, WI). All samples were collected and transported according to specifications provided by the reference laboratory. All analyses were performed blinded, without knowledge of subject diagnoses, current therapy, or targeted outcomes. This process was performed twice during the treatment, at the first day and at the last day of the treatment. The course of treatment lasted 5 to 8 days, each day consisting of 6 hours of MNRI treatment.

4.4 Statistical analysis

All statistical analyses (calculation of mean, standard deviation, percent difference, statistical significance, and effect size) were calculated in Excel. A paired t-test was used to calculate the statistical significance (α = 0.05) between pre- and post-treatment of all disease groups and all parameters. The effect size for each parameter, between groups was assessed by calculating Cohen's d. A d Value between ±0.2–0.5 is considered a small effect (Sm), ±0.5–0.8 is a medium effect (Md), a value greater than ±0.8-1.2 is a large effect (Lg), and a value greater than + 1.2 or less that -1.2 is a very large effect (VL).

4.5 The MNRI Reflex Integration therapy modality

For those participants in the Study Group Experimental arm, each treatment session was focused on a specific process of neurodevelopment. The MNRI Reflex Integration process included the following MNRI modules:

1. Reflex Repatterning – focuses on paving and improving the connectivity between the sensory and motor neurons in a reflex circuit [53, 52] that influence the sensory-motor milestones, motor programming, planning and control, and also cognitive skills [66, 49, 67].

2. NeuroStructural Reflex and Immune System Integration – focuses on improving the functions of reflexes responsible for postural control, spine flexibility, abdomen, neck and limbs musculature tone regulation, release of core tendon guard creating positive protection and the feeling of being secure. Immunomodulatory effects were aimed at improvement of functions in T-1 immunity, cytokinesis, CD-4, CD-8 and other immune cell functions, anti-inflammatory effect, and regulation of immunoglobulins (IgE, IgG and other) [50, 61, 62].

3. NeuroTactile Integration – focuses on the regulation and normalization of tactile sensitivity (hyper- or hypo-), coordination and integration of receptors, skin dermatomes, and overall peripheral and central nervous system for support of reflex repatterning and integration [67].

4. Archetype Movements Integration – focuses on the enhancement of the primary biomechanics of motor patterns (extension, flexion, rotation, stretching-compression, and other) giving support for structural aspect of numerous reflex patterns, development of automatic and consciously learned motor abilities and skills; also postural and motor control, with secondary improvement in the speed of perception, focusing, and memory, in sensory-motor integration, and cognitive functions [68].

5. Breathing Reflex Integration – focuses on the regulation and normalization of breathing reflex patterns, and the residual volume of the lungs for normal breathing and creating enough protection and survival [64].

6. Stress and Traumatic Stress Release – focuses on reflex patterns that can impact the HPA stress-axis for letting go of past negative stressors and traumas, and for trauma normalization by activation of stress hormone and neurotransmitter regulation [63, 49].

7. Proprioceptive-Cognitive Integration – focuses on improving proprioceptive-vestibular (balance) system-related reflexes for support of postural and motor control, with secondary improvement in motor-cognitive functions.

8. Oral-Motor/Visual-Auditory Reflexes Integration – focuses on improving oral-motor, articulation and speech abilities, as well as visual and auditory functions [63].

The basic goal of the MNRI module is to utilize reflex patterns for improvements of daily functioning in individuals with disruption of sensory-motor integration, increasing stress and immune system resilience, physical wellness, behavioral and emotional regulation, and cognitive skills. A typical duration of a Family Conference is eight days. The study participants receive six 50-minute sessions of MNRI therapy programs daily.

5. Conclusions

We presented compelling evidence that MNRI therapy has multi-faceted influences on the neurological and endocrine systems. Physiological homeostasis as well as immunological optimization are impacted through hormone and neurotransmitter modulation. Results show that MNRI consistently reduces and works with mechanisms of reduction of inflammation in all five analyzed groups of disorders. We propose that this physical-therapeutic, non-pharmaceutical approach is an intervention that not only reduces inflammation but modulates MAO and PMNT, therefore reducing oxidative stress, and encouraging homeostasis of excitatory neurotransmitters. Impacting oxidative stress, inflammation and optimizing neurotransmitter levels will enhance neurological and endocrine health. Imbalances of neurotransmitters will influence mood, cognitive function, focus, behavior, motivation and ability to assimilate or understand social norms. MNRI facilitates neurodevelopment, stress resiliency, neuroplasticity, and optimal learning opportunity. Note, that every study group is traditionally treated with pharmacological or invasive medical treatments, having potentially severe side effects. There have been no reported side effects of MNRI treatments.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

MNRI	Masgutova Neurosensorimotor Reflex Neuromodulation intervention
ADHD	attention deficit/hyperactivity disorder
OCD	Obsessive compulsive disorder
TAAR1	the trace amine-associated receptor
MAO	monoamine oxidase A
PMNT	phenylethanolamine N-methyltransferase
CNS	central nervous system
SNS	Sympathetic nervous system
PNS	Parasympathetic nervous system
PEA	palmitoylethanolamide
ASD	Autism spectrum Disorder
HPA	hypothalamus-pituitary-adrenal
ADD	attention deficit disorder
NMDA	N-methyl-D-aspartate receptor

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