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Treatment of Psychiatric Disorders

Highlights

A Case of GM 1 Gangliosidosis

Untangling Psychology from Biology

Discovering Thoughts, Inventing Future

VOLUME 23 ISSUE 3 VERSION 1.0

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Untangling Psychology from Biology in the Treatment of Psychiatric Disorders

By Michael Raymond Binder, M.D.

Abstract- Due to the lack of a clear distinction between mentally-driven psychiatric symptoms and neurologically-driven psychiatric symptoms, determining which patients would best be treated with psychotherapy, which patients would best be treated with pharmacotherapy, and which patients would best be treated with both is a challenge that every behavioral health clinician faces. In an effort to overcome this challenge, this article will discuss the anatomical and functional relationship between the mind and the brain as it relates to the various treatment options that are currently available and introduce a groundbreaking new paradigm that is destined to transform the treatment of mental illness from a symptom-based practice to a pathology-based practice.

Keywords: psychotherapy, medication, biomarkers, mind-brain dynamics, neuronal hyperexcitability, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, treatment options.

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Untangling Psychology from Biology in the Treatment of Psychiatric Disorders

Michael Raymond Binder, M.D.

Abstract- Due to the lack of a clear distinction between mentally-driven psychiatric symptoms and neurologically-driven psychiatric symptoms, determining which patients would best be treated with psychotherapy, which patients would best be treated with pharmacotherapy, and which patients would best be treated with both is a challenge that every behavioral health clinician faces. In an effort to overcome this challenge, this article will discuss the anatomical and functional relationship between the mind and the brain as it relates to the various treatment options that are currently available and introduce a groundbreaking new paradigm that is destined to transform the treatment of mental illness from a symptom-based practice to a pathology-based practice. In addition to putting the assessment and treatment of mental illness on par with other medication specialties, the new paradigm ushers in the first objective way to distinguish biologically-based psychiatric symptoms from psychologically-based psychiatric symptoms. This is of critical importance because it has the potential streamline treatment, better define the target for treatment, and more accurately inform the planning of treatment. It also has the potential to improve patient education and treatment outcomes by better explaining how psychotherapy works, how pharmacotherapy works, and how these two treatment modalities can complement or, in some cases, antagonize each other. Beyond all of these advantages, the new paradigm offers the potential to ward off psychiatric symptoms before they even begin. With the prevalence of psychiatric and substance use disorders at epidemic proportions, these long-awaited advances could not be more timely.

Keywords: psychotherapy, medication, biomarkers, mind-brain dynamics, neuronal hyperexcitability, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, treatment options.

I. Introduction

Both in the United States and other developed countries, the prevalence of anxiety, depression, and other common psychiatric disorders has reached epidemic proportions. Consequently, there is a desperate need for improved treatment outcomes, yet the effectiveness of mental healthcare is not much better now than it was fifty years ago [1]. Psychotherapists continue to employ various psychotherapeutic techniques, and psychiatrists continue to prescribe antidepressants, antipsychotics, and psychostimulants in various combinations. Typically, patients who have relatively mild psychiatric symptoms enter the behavioral healthcare system by consulting with a psychotherapist in the hope of avoiding treatment with medication. Patients who have more severe symptoms sometimes initiate treatment with a psychotherapist, sometimes with a psychiatrist, and sometimes with both. There are also some patients who initiate treatment with an internist and then either continue with the internist or receive a referral to a specialist. Unlike in the past, most contemporary psychiatrists do not practice psychotherapy, and most psychotherapists exhaust the benefits of their craft before referring the patient to a psychiatrist. One of the fundamental problems with this triage system is that patients largely self-select the modality of treatment they receive. Another problem is that there is no objective way to determine which patients would best be treated with psychotherapy, which would best be treated with medication, and which would best be treated with a combination of the two. Yet another problem is the potential lack of communication between the psychotherapist and the psychiatrist when both services are being provided simultaneously. These potential problems underscore the need for clinicians and prospective patients to better understand the mechanisms through which various psychotherapeutic and psychopharmacologic treatment modalities exert their therapeutic effects and to be able to determine, more objectively, which treatment modality would be most appropriate for which patient.

In this article, current psychological and biological approaches to treatment will be reviewed, and a new formulation of the dynamic interplay between the mind and the brain will be discussed. From this fresh perspective, the puzzling relationship between mental processes and neurological processes will be clarified, and a new way of conceptualizing mental illness will be proposed. Based on this new conceptualization, which is strongly supported by converging lines of evidence, the first objective method of determining which patients should be treated with which modality—psychotherapy or biological therapy—will be introduced and, by offering the potential to treat mental illness based on pathology rather than symptomatology, a new era of behavioral healthcare will be ushered in.

Author: Adult and Adolescent Psychiatry, 5 Revere Drive, Suite 200, Northbrook, USA. e-mail: mbinder@drmichaelbinder.com

II. Current Approaches to Mental Illness and How they Work

a) Psychological Interventions

i. Supportive Psychotherapy

Considered to be at the heart of all clinician-patient relationships, supportive psychotherapy encourages the patient to express his or her thoughts, feelings, and concerns in a safe, confidential, and nonjudgmental environment. Though helpful in treating almost any clinical condition, the precise mechanism (or mechanisms) through which supportive psychotherapy exerts its therapeutic effects are still not fully understood. However, its primary therapeutic mechanism appears to be stress-reduction.

ii. Psychoanalytic Psychotherapy

As the dominant form of therapy during the late 19th to mid20th centuries, psychoanalysis is aimed at helping patients resolve unconscious psychological conflicts by allowing them to become more aware of their unconscious thoughts, drives, and motives. The pioneer of this technique, Sigmund Freud, believed that as patients progressed, they became less stressed, less defensive, and, thus, less neurotic. However, the neurological correlates of these changes and their relationship to the patient's symptoms are still unclear.

iii. Interpersonal Psychotherapy (IPT)

IPT focuses on relieving psychiatric symptoms by improving interpersonal functioning and social support. The central tenant of IPT is that psychiatric symptoms are the consequence of current difficulties in one's relationships with others. Hence, the belief is that symptoms can be reduced by addressing current social stressors and helping patients develop healthier ways of relating to others. However, as with psychoanalytic psychotherapy, the effects of these changes on neurological function are still unclear.

iv. Existential Psychotherapy

Developed out of the philosophies of Friedrich Nietzsche and Søren Kierkegaard, existential psychotherapy hypothesizes that stress, frustration, and human discontent can be overcome through wisdom, willpower, and accepting personal responsibility. As a patient's stress levels decline, so too will his or her psychiatric symptoms. However, the neurological mechanism through which the patient's symptoms decline is still unknown.

v. Cognitive-behavioral Therapy (CBT)

CBT, which is commonly used for a wide range of mental health conditions, focuses on how one's thoughts, beliefs, and attitudes affect their feelings and actions. By replacing one's negative, self-defeating, and self-destructive thoughts with positive, self-affirming, and productive thoughts, one can reduce their psychiatric symptoms and literally change the way their brain processes information [2, 3]. However, the theory behind CBT does not answer the question of why some persons develop negative ways of thinking whereas others do not despite being raised in the same household by the same parents. It also fails to explain how the neurological changes that occur in conjunction with the observed cognitive and behavioral changes translate into a reduction of psychiatric symptoms.

vi. Dialectic-behavioral Therapy (DBT)

Based on the principles of CBT, DBT is specifically designed to help persons who experience their emotions too intensely. The DBT therapist helps the patient to combine opposing or "dialectic" cognitions and emotions to achieve a more positive way of thinking and feeling about things. In so doing, one's stress levels and, thus, one's psychiatric symptoms are reduced. However, DBT does not explain why, either psychologically or neuropsychiatrically, some persons experience their emotions more intensely.

vii. Biofeedback

Biofeedback attempts to reduce mental, emotional, and physical symptoms by teaching a person to control various functions of his or her body, such as heart rate, respiratory rate, and muscle tone. In theory, the meditative aspect of this discipline combines with a sense of empowerment over physical symptoms to reduce cognitive-emotional distress. Thus, biofeedback has the potential to reduce psychiatric symptoms as well as their associated physical symptoms. However, this treatment approach neither hypothesizes nor addresses the underlying cause of the symptoms.

viii. Eye Movement Desensitization and Reprocessing (EMDR)

Initially intended to help reduce symptoms of post-traumatic stress disorder, EMDR attempts to facilitate cognitive-emotional healing by alternately activating, with either voluntary eye movements or physical stimuli, the left and right sides of the body and then asking the patient to capture and hold in his or her mind, while the alternating stimulus is repeated, whichever thoughts and emotions were experienced. Although the mechanism by which EMDR exerts its therapeutic effects is not fully understood, the technique is thought to activate some of the same neurological recovery processes that occur during rapid eye movement (REM) sleep.

ix. Mindfulness Meditation

In mindfulness meditation, patients are asked to step back and reflect on the way they are thinking and feeling about individual emotional stressors and before they respond to them. This allows them to gain insight into their attitudes and behaviors and to develop a higher degree of self-discipline and self-control. Included in the technique are breathing exercises, guided imagery, and other practices that help relax the

mind and body. Through this relaxation processes, psychiatric symptoms are reduced and one's self-confidence is increased. However, the neurological mechanism through which this healing takes place remains unclear.

b) Medical Interventions

i. *Psychotropic Medications*

a. *Antidepressants*

Antidepressants are the mainstay of treatment for anxiety, depression, and a number of related psychiatric disorders. The serendipitous discovery of the antidepressant effect back in the 1950s led to the monoamine hypothesis of depression, which posited that a deficiency of monoamines was the core abnormality in clinical depression [4]. Although this could not explain why the antihypertensive drug reserpine, which lowers the activity of monoamines, was likewise effective in reducing symptoms of depression [5], the monamine hypothesis has guided the use of antidepressants for more than fifty years. More recently, however, several other weaknesses of the monoamine hypothesis have been identified. Chief among these are its failure to explain how antidepressants can be effective in treating psychiatric disorders other than clinical depression [4]; why a depletion of serotonin precursors does not produce symptoms of depression in healthy subjects [6]; and why antidepressants can sometimes cause a paradoxical worsening or cycling of symptoms [7-10]. It also fails to explain how the purported abnormalities in monoamine transmission actually translate into depressive symptomatology [11].

b. *Antipsychotics*

Also known as "major tranquilizers," antipsychotic drugs were originally used to treat agitation, hallucinations, and delusions in schizophrenia. However, they are increasingly being used to augment the effects of antidepressants and mood stabilizers in the treatment of clinical depression and bipolar disorder. Pharmacologically, antipsychotic drugs exert a host of neuroinhibitory effects, including blockade of histamine, dopamine, norepinephrine, and acetylcholine receptors [12], and although dopamine is known to play an important role in auditory signaling [13], the precise mechanism by which antipsychotic drugs exert their wide-ranging therapeutic effects has heretofore remained unclear.

c. *Psychostimulants*

Although these drugs were initially used to treat ADHD, they are now being used to treat a variety of co-occurring symptoms, such as anxiety, depression, apathy, and drowsiness. Psychostimulants are thought to exert their therapeutic effects by increasing catecholaminergic transmission in the brain. However, as with antidepressants and antipsychotics, the precise mechanism by which their pharmacological effects translate into their cognitive-emotional effects remains unclear.

d. *Anticonvulsants*

More commonly known in psychiatry as "mood stabilizers," the use of anticonvulsants is largely reserved for bipolar spectrum disorders because of their ability to stabilize mood. Although the precise mechanism by which they exert this clinical effect has heretofore remained unclear, anticonvulsants are known to reduce neuronal excitability by a number of mechanisms, including augmentation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [14], potentiation of GABA receptor activation [15], and reduction of sodium and calcium flux across neuronal membranes [16, 17].

e. *Ketamine*

In recent years, ultra-low doses of the dissociative anesthetic ketamine have been found to exert some of the most rapid and robust antidepressant effects yet to be observed [18]. Unfortunately, however, ketamine is relatively short-acting, has a narrow therapeutic index, and can be cumbersome to administer [19]. With repeated dosing, it also carries the risk of cognitive impairment, tolerance, and withdrawal [19]. However, the rapid and robust therapeutic effects of ketamine have drawn intense interest to its pharmacological effects. The drug is known to be an antagonist of the excitatory neurotransmitter glutamate, thus implicating glutamate in the pathophysiology of depression and possibly other psychiatric disorders.

f. *Neuroactive Steroids*

Recognizing that the postpartum period is a time of both increased vulnerability to depression and sharp fall in serum progesterone levels, derivatives of progesterone are now being investigated for use in treating clinical depression and bipolar disorder [20-22]. Although preliminary data look promising, a potential limitation of these drugs is a loss of therapeutic effect over time. This concern is based on previous experience with other positive allosteric modulators of the GABA-A receptor, such as barbiturates, benzodiazepines, and sedative hypnotics, all of which carry the risk of tolerance, dependence, and withdrawal. However, the therapeutic success of GABA-A receptor modulators, which put a break on neuronal firing, reiterates the importance of calming the brain in the treatment of psychiatric disorders.

ii. *Somatic Therapies*

a. *Electroconvulsive Therapy (ECT)*

Still regarded as the gold-standard in the treatment of clinical depression, ECT involves the intentional induction of seizure activity in the brain. Although the mechanism by which ECT exerts its therapeutic effects remains unclear, it is evident that clinical improvement occurs not during the seizure but in

the aftermath of the seizure. It is now recognized that seizures are brought to a halt by a host of neuroinhibitory changes that occur in response to the seizures themselves. Known inhibitory mechanisms include glutamate depletion, GABAergic recurrent inhibition, membrane shunting, depletion of energy stores, loss of ionic gradients, endogenous neuromodulator effects, and regulatory input from various brain regions [23]. Hypothetically, this cascade of neuroinhibitory responses explains why ECT is an effective treatment for status epilepticus [24, 25]. Also, based on the known psychotherapeutic effects of calming the brain, the need for a cumulative effect could explain why a course of several ECT treatments is typically needed to achieve a substantial and lasting reduction of psychiatric symptoms. Since its introduction in the late 1930s, the use of ECT has expanded to bipolar disorder, delusional disorder, obsessive-compulsive disorder, schizophrenia, schizoaffective disorder, catatonic states, and neuroleptic malignant syndrome [26], thus reiterating the wide-ranging therapeutic effects of calming the brain and suggesting that many psychiatric disorders could have a shared pathophysiology.

b. *Repetitive Transcranial Stimulation (rTMS)*

As one of the newest techniques for treatment-resistant depression, rTMS uses electromagnetic induction to non-invasively depolarize or hyperpolarize neurons in the brain. Consistent with the idea that specific neurological processes affect the corresponding cognitive-emotional processes, rTMS is thought to exert its therapeutic effects by modulating the activity of specific neuronal circuits [27].

c. *Deep Brain Stimulation (DBS)*

Also known as "brain pacemaker," DBS involves the selective stimulation of specific brain areas via an implanted electronic device. The technique is thought to exert its therapeutic effects by correcting the firing imbalances of neuronal circuits that are believed to be associated with the patient's symptoms. Thus, for example, in severe intractable depression, symptoms are thought to be relieved by stimulating brain areas that would normally be more active in non-depressed persons. This mimics the effects of psychotropic drugs and rTMS in that it modulates neuronal signaling.

d. *Vagus Nerve Stimulation (VNS)*

VNS is another "pacemaker" technique that involves the surgical implantation of electrodes (in this case into the chest) to stimulate specific circuits in the brain. It is used in the treatment of seizure disorders, mood disorders, and chronic pain that is resistant to pharmacotherapy. After the VNS device is inserted under the skin, a wire is connected to the vagus nerve in the neck. Through this connection, the neurostimulator delivers thirty-second pulses of electricity to the vagus nerve, which feeds into the solitary tract nucleus. Affarrents of the solitary tract increase the activity of the inhibitory neurotransmitter GABA while at the same time reducing the activity of the excitatory neurotransmitter glutamate. Solitary tract affarrents also promote norepinephrine signaling via projections to the locus coeruleus and amygdala [28]. This combination of effects is thought to explain the therapeutic effects of VNS in treatment-resistant depression.

e. *Stellate Ganglion Block (SGB)*

SGB is now being used to treat a number of conditions, including complex regional pain syndrome, high blood pressure, and some psychiatric disorders, particularly post-traumatic stress disorder [29]. The stellate ganglion is present in approximately 80% of the general population and is composed of the inferior cervical ganglion and the first thoracic ganglion fusion. It is located posteriorly in the neck at the level of the seventh cervical vertebra. SGB involves anesthetizing the stellate ganglion so as to reduce the sympathetic outflow that is relayed through it. In so-doing, the ratio of sympathetic-to-parasympathetic output is reduced, thus helping to quell the flight-or-flight response. As with nearly all of the aforementioned medical interventions, symptom reduction occurs in association with calming the nervous system, thus reiterating the therapeutic value of neuroinhibition in the treatment of psychiatric symptoms.

III. A New Way of Conceptualizing Mental Illness

a) *Anatomical and Functional Relationship Between the Mind and the Brain*

With the birth of neuroscience, the historical idea that the soul was the seat of thoughts and emotions was replaced with the reductionist idea that thoughts and emotions were the products of complex brain function. However, a burgeoning number of eye-witness reports and testimonials from around the world is beginning to reawaken the idea that consciousness is possible both in conjunction with and independent of brain function. There are now millions of people from diverse ethnic, cultural, and religious backgrounds who claim to have had vivid out-of-body experiences during a close brush with death or, in some cases, an actual pronouncement of death [30-35]. During these so-called near-death experiences (NDEs), those who have had them claim to have left their physical bodies and continued to think, perceive, and remember things that, based on the reductionist view, would have been physically impossible [30-35]. Moreover, many of these accounts have been corroborated by factual information that the NDErs could not possibly have known had they not actually separated from their physical bodies and retained their cognitive, sensory, and memory functions [30-35]. The evidence is now so strong that, in 2022, the New York Academy of Sciences published a

multidisciplinary consensus statement concluding that "NDEs are not hallucinations or illusions but rather evidence that life continues after death" [36].

According to NDErs, the mind, when separated from the body, is even more lucid, more aware, and more knowledgeable than when it dwells in the body. This suggests that the brain, rather than being the extraordinary information processor that it has been touted to be, is actually slowing down and limiting mental function. However, what NDErs also report is that they were unable to interact with the physical world while outside their physical bodies. Thus, the brain appears to be acting as a biological transducer that translates mental signals into neurological signals. The reverse process also appears to occur: the brain appears to stimulate specific thoughts and emotions in the mind, thus creating a two-way dialogue between the mind and the brain.

That this mind-brain dialogue actually occurs has now been demonstrated experimentally. Recording from single neurons in patients implanted with intracranial electrodes for clinical reasons, Cerf et al. [37] found that willful thoughts and emotions readily stimulated specific neurons when subjects were asked to perform specific mental tasks. Conversely, stimulating different parts of the brain with an electrical probe has long-been known to trigger different thoughts and emotions [38]. However, this mind-brain dialogue gives rise to the historic mind-body problem: how can the mind and the body communicate with each other if their natures are different? The answer to that question may be supplied by modern advances in biology, chemistry, and physics.

Like all forms of energy, mental energy would be expected to induce magnetic fields. Likewise, the neurons of the brain induce magnetic fields as they depolarize and repolarize. Hence, the mind and the brain are naturally poised to communicate in the same language—electromagnetic energy. Besides helping to explain both the emerging data on NDEs and the experimental observations of Cerf and his colleagues, a duality of mind and brain could, for the first time, explain the distinction between unconscious and conscious mental processing. Unconscious mental processing would occur independent of brain function, whereas conscious mental processing would occur when neurologically-induced magnetic fields synchronized with mentally-induced magnetic fields (Figure 1). This synchronization process hypothetically explains the familiar time-delay when the mind attempts to formulate a thought or draw a memory into consciousness. Consciousness, in this sense, could more aptly be called "corporeal consciousness" because it occurs in conjunction with neurological function. This is in contrast to "incorporeal consciousness," which would occur independent of neurological function [11]. Note also that unconscious mental processing, being electromagnetic but independent of neurological function, would proceed at a speed of approximately 300,000,000 meters/second (the speed of electromagnetic waves). This is in contrast to conscious mental processing, which, being dependent upon neurological function, would proceed at the relatively slow speed of about 150 meters/second (the speed of salutatory conduction) [39]. This difference, together with the uncoupling of the mind from bodily sensory systems during an NDE, could explain why NDEers experience such a dramatic expansion of consciousness when they separate from their physical bodies [31-34].

Further evidence that the mind is capable of functioning independent of the brain comes from the observation that children who are born without a cerebral cortex are conscious [40], and in their pioneering work, Wilder Penfield and others found that awareness of self and environment were fully preserved as they surgically removed relatively large areas of the cortex to treat refractory seizures [40, 41].

That leads to the question of where in the body the mind is located. Based on the observation that injury to anybody-part other than the head leaves corporeal consciousness intact, it is evident that the mind is located in the head. Also, with the exception of damage to the neurological system, damage to any part of the body can be perceived by the mind. That implies that the mind-body connection must be dependent upon intact neurological function. The only part of the neurological system that is in the head is the brain. Therefore, the mind-body connection must occur in the brain.

Although it would be difficult to pinpoint where in the brain the mind is located, the topography and functional anatomy of the brain provide important clues. It is well-recognized that virtually all sensory input is relayed directly to the thalamus. It is also known that the thalamus remains a part of the conversation as the input is being processed by the cerebral cortex and other parts of the brain [42]. Furthermore, even mild damage to the thalamus can result in a vegetative state [43]. Conversely, deep brain stimulation of the thalamus has been found to be of some benefit in rousing patients from a minimally conscious state [44, 45]. Hence, it appears that the thalamus, which has been called "the gateway to the mind," could be acting as a functional interface that allows the mind to monitor and control virtually every function of the brain and body [11]. That would place the mind, or at least its primary area of focus, at the core of the brain.

Mind-Brain Interactions

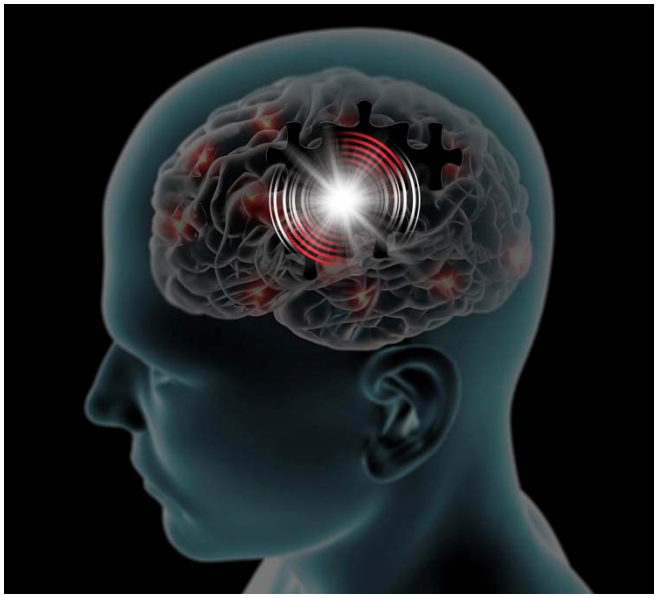

Figure 1: Schematic illustration of the mind (large white burst) communicating with the brain via the synchronization of mentally-induced magnetic fields (white radiations) and neurologically-induced magnetic fields (red radiations).

b) Practical Application of Mind-Brain Dynamics to the Diagnosis and Treatment of Mental Illness

The idea that the mind and the brain are two distinctly different entities that interact with each other could begin to explain how treatment with psychotherapy alone and medication alone can achieve similar results both psychologically and neurologically [46]. Therapies that are aimed directly at changing the way one thinks would have secondary affects on the brain because everything that is processed by the mind would simultaneously be processed by the brain. Conversely, therapies that are aimed directly at modulating brain function would have secondary effects on the mind because everything that is processed by the brain would simultaneously be processed by the mind. Thus, for example, cognitive-behavioral therapy, which changes the way one thinks and feels, would retrain circuits in the brain because changes in cognitive-emotional processing alter neuronal firing patterns. Conversely, pharmacological therapy, which modulates the activity of specific neuronal circuits, would retrain one's thoughts and emotions because changes in neuronal signaling cause changes in mental and emotional processing.

The big question when it comes to therapy, however, is which form would be most effective for which patient? To answer that question, one would first need to determine which of the two—the mind or the brain—was the primary driver of the symptoms. One would then need to determine which form of therapy, when used to treat the appropriate part of the cognitive-emotional system, would be best for which patient. However, the answer to both of these questions would depend upon an accurate understanding of what causes psychiatric symptoms to begin with.

Although the precise cause of psychiatric symptoms remains unclear, an emerging hypothesis contends that psychiatric symptoms are driven by pathological hyperactivity in symptom-related circuits in the brain. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, pathological hyperactivity in anxiety circuits causes elevated and persistent feelings of anxiety; pathological hyperactivity in depressive circuits causes elevated and persistent feelings of depression; and pathological hyperactivity in cognitive circuits causes racing thoughts and obsessional thinking [47]. Yet, that would still fall short of explaining why the symptom-related circuits in the brain become pathologically hyperactive.

However, a possible answer to that question is supplied by the gene research. A number of large, multi-center gene association studies have found that persons who suffer from common psychiatric disorders, such as anxiety, depression, bipolar disorder, and schizophrenia, have gene variants whose protein products fail to adequately regulate the firing of neurons [48-61]. Now then, given that all of the most common psychiatric disorders are essentially different combinations of the same symptoms, it would not be unreasonable to think that all of these disorders could be rooted in a shared physiological abnormality; namely, neuronal hyperexcitability. Hyperexcitable neurons would just fire too easily and fail to shut off when they should. Indeed, this aligns with the neurophysiological abnormalities that have been

observed on functional [62] and electroencephalographic [63] studies of depression.

Now imagine that an affected person were confronted with a stressful situation. The hyperexcitability of the neurons would cause all of the person's anxious thoughts to run through his or her mind more times than they should, and it would cause all of the person's uneasy emotions to be abnormally intense and persistent. In addition to being experienced as inappropriately excessive worry and anxiety, the added mental and emotional tension would cause the related circuits in the brain to be further stimulated, thus creating a vicious cycle of mutual overstimulation between the mind and the brain. Moreover, this vicious cycle would, over time, be further amplified by "primed burst potentiation," a natural kindling effect through which neurons that are repeatedly stimulated become increasingly responsive to further stimulation [64].

Another factor that would add fuel to the fire is the tendency for neuronal circuits to compete for dominance. From the study of epilepsy, it is known that pathologically hyperactive circuits tend to inhibit the activity of competing circuits [65]. This phenomenon would tend to prevent the mind from shifting attention to less anxious and more productive thoughts. In other words, it would leave the mind and the brain caught in the "default mode," a psychophysiological state of unproductive internal processing that has been observed on functional imaging of clinical depression and other neuropsychiatric disorders [66]. It could also lead to aberrant circuit induction. This process, which is analogous to a short-circuit in a wired electrical system, hypothetically involves the inappropriate stimulation of relatively hypoactive circuits by pathologically hyperactive circuits [67]. As the feeder circuits quiet down due to synaptic fatigue [68], the freshly activated receiver circuits cause the person's thoughts and emotions to shift accordingly, thus driving the "bipolar switch" [67]. With all of this abnormal electrical activity hijacking the cognitive-emotional system, it is not surprising that affected persons are so easily overwhelmed, so emotionally unstable, and so plagued with self-doubt.

This raises the question of what really drives patients to seek treatment. The natural assumption is that they are driven to seek treatment by the factors that they say drove them to seek treatment. However, as one can see from the forgoing discussion, those factors can be abnormally amplified and distorted by poorly restrained discharges from the brain. Yet in actual practice, neither patients nor their healthcare providers have any reliable way of knowing this. In the 1900s, mild cognitive-emotional distortions were referred to as "neuroses," and severe cognitive-emotional distortions are still referred to as "psychoses." According to the MCNH hypothesis, various forms of psychosis are created when, due to the amplifying effect of neuronal hyperexcitability, the intensity of mentally-generated thoughts and emotions becomes as high or higher than the intensity of thoughts and emotions that would normally be driven by input from the eyes, ears, and other sensory organs. Hypothetically, the margin between internally-driven thoughts and emotions, which are normally of lower intensity, and externally-driven thoughts and emotions, which are normally of higher intensity, is what allows a person to distinguish internal from external reality. Of course, the distorting effect of neuronal hyperexcitability can easily be recognized in severely psychotic patients; but the distorting effect can be more difficult to recognize in patients whose complaints are less out-of-line with reality. If the therapist then begins to work with this distorted content in such patients, he or she would unwittingly be attempting to treat a neurological problem with a psychological intervention. By analogy, it would be like trying to correct impaired vision by talking about it. The difference, however, is that talking about a visual impairment cannot do further damage to the eye; whereas, talking about neurologically-distorted thoughts and emotions can cause further damage by continuing to stir the pot, particularly in a person whose hyperexcitable brain is continuing to distort everything that he or she thinks and feels. Most experienced psychotherapists can readily attest to the risk of regression when intensive psychotherapy is attempted with more severely disturbed patients (presumably those with higher levels of neuronal hyperexcitability), and the renowned Austrian psychiatrist Sigmund Freud, due to the same concerns, was careful to avoid psychoanalyzing psychotic-range patients [69].

In contrast to persons with hyperexcitable brains, those with normoexcitable brains would be relatively resistant to cognitive-emotional stress, and they would be even more resistant to developing psychiatric symptoms. That raises the possibility that most, if not all, persons who present for psychotherapy have hyperexcitable brains. Additional support for this idea comes from the observation that the vast majority of persons who initially seek the care of a psychotherapist rarely need to continue psychotherapy once, upon being referred to a prescriber, their neurological function is normalized with anticonvulsant drugs. Another observation that suggests that most persons who seek psychotherapy have hyperexcitable brains is that such persons are rarely satisfied with their treatment until they either become willing to accept medical therapy or they establish natural brain-calming habits and routines, such as stress-reduction, establishment of an early sleep schedule, regular exercise, avoidance of psychostimulants, and minimization of refined sugar. Consistent with this observation, the Royal Australian and New Zealand College of Psychiatrists is now, for the first time, recommending attention to diet, regular exercise, and

sleep hygiene as "non-negotiable first steps" in the treatment of major depressive disorder [70].

Another important factor to consider is that the majority of studies that compare the effectiveness of psychotherapy alone to pharmacotherapy alone involve the use of antidepressants, and antidepressants are not the appropriate treatment for neuronal hyperexcitability [67, 71, 72]. Still, such studies yield comparable results [73], an observation that calls psychotherapy into question as much as the use of antidepressants. That is not to say that psychotherapy, as a therapeutic tool, is unhelpful, but only to say that most persons who seek psychotherapy would be better served if they were to simultaneously be assessed for neuronal hyperexcitability. If this common condition could be identified and treated successfully early in the course of psychotherapy, the distorting element of the patient's distress would be minimized, and the therapy could focus more on matters that truly were rooted in psychology, such as attitude, values, and priorities. Some of the aforementioned psychotherapeutic techniques do just that, whereas others analyze the patient's distressing thoughts and emotions.

What all of the psychotherapeutic techniques have in common, however, is that they aim to reduce intrapsychic tension. Reducing intrapsychic tension has both direct and indirect benefits; it benefits the mind directly by bringing psychological relief, and it benefits the brain indirectly by reducing mental stimulation of the brain. However, as previously discussed, intrapsychic tension can be difficult to reduce when the pathologically hyperactive brain is keeping the mind bathed in stress. That underscores the importance of pharmacotherapy. If the brain could be quieted directly through anticonvulsant drugs (or any of the aforementioned medical therapies), the interference from the brain would be reduced, thus explaining why medical therapy tends to work faster than psychotherapy [46] but not as well as when combined with psychotherapy [74].

Notwithstanding the potential benefits of medical therapy, it should be noted that antidepressants, psychostimulants, and some of the other medical therapies that were referenced earlier stimulate some parts of the brain while calming others. For example, SSRIs increase neuronal firing in the cerebral cortex [75] but reduce neuronal firing in the amygdala [76], and rTMS can be used to either stimulate or inhibit the activity of specific neuronal circuits [77, 78]. Although increasing the activity of specific circuits can be therapeutic, it can also be counter-therapeutic, depending on how it affects the circuit-specific imbalances that are driving the patient's symptoms. This is the MCNH explanation for the paradoxical effects that neuroactivating medical therapies, particularly antidepressant and psychostimulant therapies, can have. With these two classes of drugs topping the list of the most commonly prescribed medications, and the prevalence of psychiatric and substance use disorders at epidemic proportions, the need to better understand how these drugs and other medical therapies are affecting the mind and brain is evident.

IV. Assessing the Relative Importance of the Neuronal Hyperexcitability Trait

But even if neuronal hyperexcitability were at the root of psychiatric symptoms, it would not discount the importance of numerous other factors, such as family upbringing, childhood trauma, ongoing stressors, and personal choices. However, an analysis of the family pedigrees of persons who exhibit signs of mental illness is quite revealing. Although family, twin, and adoption studies have historically failed to identify a classic Mendelian pattern of inheritance for any of the common psychiatric disorders, a reconceptualization of psychiatric symptomsas the symptomatic expression of the neuronal hyperexcitability trait does reveal a classic Mendelian distribution. That distribution is strikingly autosomal dominant! [47]. In other words, in those families that are affected, probands who develop either subsyndromal or more obvious signs and symptoms of mental illness, such as a diagnosable psychiatric, functional physical, or substance use disorder, almost always appear in a classic autosomal dominant distribution. Moreover, a predictable subset of children in these families are completely unaffected despite being raised in the same households by the same parents. These so-called "survivors," who typically appear in an autosomal recessive distribution, are presumably those who did not inherit one of the gene variants that have been linked to neuronal hyperexcitability. These observations combine to suggest that: 1) all of the most common psychiatric and functional physical disorders are rooted in the same biological abnormality; 2) all of these disorders may be driven by polymorphisms of a single gene locus; and 3) the hypothesized abnormality may be the most important predisposing factor in the development of these disorders. While recognizing their profound importance, these observations should be interpreted with caution because they are based on informally-obtained family pedigrees (approximately 300) rather than tightly controlled studies [67, 79].

V. The Challenge of Identifying the Neuronal Hyperexcitability Trait

Although the phenomenon of neuronal hyperexcitability as a possible driver of psychiatric symptoms has been described previously [47, 80], its significance has been sorely overlooked. This is largely due to the elusive nature of the neuronal hyperexcitability trait. The reasons for the difficulty

identifying the trait are complex and multi-faceted. Some, but not all, will be discussed here for the purpose of illustration.

The most fundamental reason that the neuronal hyperexcitability trait has been so difficult to identify is that the trait has heretofore been undetectable by any form of laboratory testing, neuroimaging, or electroencephalography. Hyperexcitable neurons, like a hive of irritable bees, cannot be distinguished from normoexcitable neurons until the metaphorical bees are disturbed. However, even then, the brain does not become hyperactive as a whole. Rather, the pathological hyperactivity occurs in the brain's microcircuitry [81], where it can easily be overlooked or considered to be normal on diagnostic studies. The same challenge is experienced clinically, as carriers of the trait can be completely asymptomatic until something or someone begins to stress them. However, even when symptoms begin to appear, they are commonly accepted as normal both because the neuronal hyperexcitability trait is harbored by such a large fraction of society and because the symptoms primarily involve the same cognitive-emotional states that every person may experience from time to time.

Another reason that the neuronal hyperexcitability trait has remained so difficult to identify is that stress-inducing circumstances are highly specific to the individual and, in most cases, only really known by the individual. This makes it difficult to assess the appropriateness of the symptoms to the circumstances that seem to precipitate them. Also, due to the variable time-course of kindling, symptom-onset can be delayed by days, weeks, or months [82], thus adding to the difficulty of assessing the appropriateness of the symptoms.

Yet another reason that the neuronal hyperexcitability trait has remained so elusive is that the diagnosis of psychiatric disorders has traditionally been symptom-based rather than pathology-based. Hence, the signs and symptoms of neuronal hyperexcitability, which can be highly diverse due to the high diversity of neuronal circuits and firing patterns, are generally viewed as different syndromes rather than as exacerbations of a shared neurophysiological abnormality [83, 84]. This, in turn, has treatment implications that can lead clinicians even further down the wrong path due to current prescribing habits. Since the development of the monoamine hypothesis of depression, prescribers have been strongly entrained to treat most psychiatric disorders with antidepressants. However, based on resting vital-sign measurements (the diagnostic value of which will be discussed later), the neuronal hyperexcitability trait is harbored by approximately 4 out of 10 persons [67, 85, 86]. This estimate is corroborated by the fact that anticonvulsants and other brain-calming drugs had, throughout most of recorded history, been the mainstay of medical treatment for a wide range of emotional and physical ailments [87]. Today, in the wake of the antidepressant revolution, the use of anticonvulsants has been relegated to bipolar spectrum disorder [67, 88]. The problem with this diagnostically-based change is that bipolar spectrum disorder is often misdiagnosed as unipolar depressive disorder [89-92]. This error is further complicated by the fact that antidepressants can have beneficial effects in bipolar spectrum patients despite the fact that they do not address the core physiological abnormality in the disorder [72]. All of these barriers to recognizing the neuronal hyperexcitability trait underscore the need to more easily identify the trait.

VI. Toward an Objective Method of Identifying the Neuronal Hyperexcitability Trait

In recent years, an explosion of clinical studies has identified an association between resting vital-sign measurements and the later development of various psychiatric and general medical conditions. In a longitudinal study involving more than one million men in Sweden, Latvala et al. [93] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [94] found that adolescent girls with emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of chronic physical illnesses, including diabetes [95-98], high blood pressure [99-101], cardiovascular disease [102-107], cerebrovascular disease [108-110], cancer [110-112], dementia [113], and all-cause mortality [110, 114]. The subtle vital-sign elevations with which these illnesses are associated are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [115]. This is the MCNH explanation for why the lifespan of persons with severe mental illness tends to be much shorter than the general population [115]. The reason that psychiatric and "functional" physical symptoms would tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and systems of the body [116]. The physical consequences would tend to be delayed because they would express the gradual erosive effects of neuronal hyperexcitability, which can take years or even decades to occur [115]. Thus, there is mounting evidence that the neuronal hyperexcitability trait can be identified objectively [67, 115]. It has been estimated that, in the absence of any significant cardiorespiratory disease, confounding medications, or substances of abuse, an RHR above 75

beats/min or an RRR above 15 breaths/min is indicative of the neuronal hyperexcitability trait. Parenthetically, in the more than 100 consecutive outpatients that have been studied thus far, resting heart and respiratory rate measurements have proven to be more sensitive in detecting the neuronal hyperexcitability trait than formal clinical assessments.

VII. Discussion

The goal of this review was to address the question that every behavioral health clinician faces—that of deciding whether a patient should be treated with psychotherapy, medical therapy, or a combination of the two. Short of an objective way for either the patient or the clinician to make this determination, self-referral is generally the decisive factor in determining which type of therapy a patient receives, at least initially. As discussed earlier, this is potentially faulty because most patients have limited insight into the psychophysiological underpinnings of their distress, and even experienced clinicians are often unable to tell how much of the patient's distress is rooted in psychological factors and how much is rooted in biological factors. However, the idea that the inherited trait of neuronal hyperexcitability can drive the same symptoms as purely psychological factors, taken together with the idea that the trait can be identified through resting vital-sign measurements, has the potential to objectivize, for the first time, which type of therapy—psychological or biological—a patient should receive. It also has the potential to determine what percentage of patients who present for behavioral health services are carriers of the neuronal hyperexcitability trait.

Under the current system of referral and treatment selection, many patients may be receiving the wrong type of therapy. Some may be receiving psychotherapy when they should be receiving medical therapy, and some may be receiving medical therapy when they should be receiving psychotherapy. There may also be some who are receiving one form of therapy or the other when in fact they should be receiving both forms of therapy simultaneously. Also, because the neuronal hyperexcitability trait continues to be so elusive, some patients may be receiving the wrong type of medication [71, 87, 117].

Fortuitously, all of this could be about to change with the growing recognition that resting vital-sign measurements offer an objective way to determine which form of treatment a patient should receive. Beyond that, recognizing neuronal hyperexcitability as the core abnormality in mental illness could bring with it a highly treatable biological target. This too would be a first in psychiatry because the current system of diagnosis and treatment is symptom-based rather than pathology-based. Guided by the MCNH hypothesis, any patient who was determined, based on resting vital-sign measurements, to have a hyperexcitable brain could first be educated about the natural ways to calm the brain, such as stress reduction, establishment of an early sleep schedule, regular exercise, and the other lifestyle habits that were discussed earlier. Patients with moderate-to-severe symptoms could also be offered anticonvulsant therapy, as the degree of improvement achieved through lifestyle changes alone is typically limited to about 20%. Anticonvulsants, which, based on their putative mechanism of action, could more aptly be called "neuroregulators" [118], go right to the root of the problem. They reduce the excitability of the neurological system, thereby compensating for the gene abnormality that is believed to underlie the neuronal hyperexcitability trait. Moreover, unlike commonly prescribed medications, such as antidepressants, psychostimulants, and antipsychotics, all of which alter the activity of specific receptors and circuits in the brain, neuroregulators simply normalize brain function. This is a healthier approach because the brain, in most of the common psychiatric disorders, is not misfiring but rather over-firing. Hence, if a given neuroregulator were ineffective at reducing symptoms, it could appropriately be replaced with another neuroregulator rather than switching to a different class of drugs; and if one neuroregulator were only partially effective, a second one could be added, and so on. This approach, which could be called "focused neuroregulation" [119], would optimize the effectiveness of neuroregulators and minimize the need for medications that can have unpredictable, conflicting, and sometimes paradoxical effects [7, 72, 117]. As for those patients whose resting vital signs fell below the minimum cutoffs, psychotherapy alone could be recommended as first-line treatment. In such cases, the therapy would be addressing a problem that was fundamentally psychological rather than just helping a patient cope with a problem that was fundamentally neurological. Thus, the MCNH hypothesis in conjunction with resting vital-sign measurements has the potential to fast-track patients to the most efficient and effective treatment approach. Moreover, because resting vital signs can be measured in the comfort of one's own home, prospective patients would be able to perform the initial screening themselves. In an era of cellphones, smart watches, and a host of new health-tracking devices, this triage system could not be any easier or more practical.

VIII. Directions for Future Research

Urgently needed are clinical studies aimed at determining the effectiveness of focused neuroregulation in those patients who, irrespective of their DSM diagnosis, present with an RHR above 75 beats/min or an RRR above 15 breaths/min. This approach would allow researchers to circumvent the problem of overlapping and co-occurring diagnoses

and focus on determining which psychiatric symptoms would be most responsive to focused neuroregulation. A high response rate would help validate the use of resting vital-signs as markers of neuronal hyperexcitability. Also, by calculating the fraction of patients who exceed the resting vital-sign cutoffs, insight could be gained into the epidemiology of neuronal hyperexcitability and the sensitivity of resting vital-sign measurements as biomarkers of the neuronal hyperexcitability trait. If promising, such pilot studies could be followed by head-to-head prospective studies comparing the short and long-term effectiveness of this objectively-based method of diagnosis and treatment to standard (symptom-based) treatment.

Additionally, because resting vital signs appear to be constitutionally elevated in carriers of the neuronal hyperexcitability trait [93], prevention studies could be done to determine the benefits of prophylactic neuroregulator therapy in those members of severely affected families who have upper-end-of-normal resting vital signs but have not yet manifested any clear evidence of mental illness. Adjustments of prophylactic medication in such persons could be guided by the response of resting vital signs to the medication and by reassessing for signs and symptoms that may become more clinically apparent only after they are reduced. Also in these studies, the relative importance of resting vital signs as predictive markers of mental illness and the specificity of these markers could be determined by tracking the progress of siblings whose vital signs fell below the hypothesized cutoffs as well as those whose resting vital signs fell above the hypothesized cutoffs but who decided against prophylactic therapy.

Finally, to validate the hypothesis that the vulnerability to developing any of a wide range of psychiatric and functional physical symptoms is rooted in polymorphisms of single gene loci, comprehensive family diagnostic studies could be performed to determine the inheritance pattern of these symptoms and their associated psychiatric disorders as a clinically heterogenous but genetically related group. A classic Mendelian distribution would provide further support for the MCNH hypothesis and potentially pave the way for future research using CRISPR-Cas9 technology [120], offering exciting possibilities for targeted gene therapies [121].

IX. Conclusion

By recognizing the cognitive-emotional system as a dynamic interplay between mind and brain and reconceptualizing psychiatric symptoms as pathological hyperactivity in symptom-related circuitsin the brain, the MCNH hypothesis, in conjunction with resting vital-sign measurements, has the potential to revolutionize the treatment of mental illness. Rather than treating patients based on subjective assessments and personal skill sets, treatment selection could, for the first time, be based on quantitative biomarkers. Resting vital-sign measurements provide an objective, evidence-based, and easily accessible way to identify the neuronal hyperexcitability trait, an inherited neurophysiological abnormality that is hypothesized to be at the root of most psychiatric and functional physical symptoms. In addition to improving diagnostic accuracy and guiding treatment selection, targeting the neuronal hyperexcitability trait informs the use of focused neuroregulation, a safer, faster, and more effective treatment approach for those patients who are determined, based on resting vital-sign measurements, to have a biologically-based psychiatric disorder. By identifying the neuronal hyperexcitability trait, the challenge of overlapping and co-occurring psychiatric diagnoses is circumvented and the use of medications that have unpredictable, conflicting, and sometimes paradoxical effects can be minimized. Targeting the neuronal hyperexcitability trait also has the potential to ward off psychiatric symptoms before they even begin and reduce the risk of developing any of the wide range of chronic health conditions with which this highly prevalent trait has been associated. In short, the MCNH hypothesis, in conjunction with resting vital-sign measurements, has the potential to change the face of modern psychiatry by transforming the treatment of mental illness from a symptom-based practice to a biologically-based practice. By seizing this unprecedented opportunity, we can strive toward a future in which behavioral healthcare, like other fields of medicine, is aimed at specific pathological processes, thus streamlining care, speeding recovery, and overcoming the long-held stigma of mental illness.

Conflicts of Interest

The author declares that he has no competing interests.

References Références Referencias

1. Insel TR, Wang PS. The STAR*D trial: Revealing the need for better treatments. Psychiatric Services 2009. https://doi.org/10.1176/ps.2009.60.11.1466.
2. Saxena S, Gorbis E, O'Neill J, et al. Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder. Mol Psychiatry 2009; 14 (2): 197-205.
3. Lazaridou A, Kim J, Cahalan CM, et al. Effects of cognitive-behavioral therapy (CBT) on brain connectivity supporting catastrophizing in fibromyalgia. Clin J Pain 2017; 33 (3): 215-221.
4. Hirschfeld R. History and evolution of the monoamine hypothesis of depression. Journal of Clinical Psychiatry 2000; 61 (6): 4-6.
5. Strawbridge R, Javed RR, Cave J, Jauhar S, Young AH. The effects of reserpine on depression: A systemic review. Journal of Psychopharmacology 2022.

6. Neumeister A, Nugent AC, Waldeck T, et al. Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. Arch Gen Psychiatry 2004; 61: 765-773.
7. El-Mallakh RS, Vöhringer PA, Ostacher MM, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. Journal of Affective Disorders 2015; 184: 318-321.
8. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disorders 2001; 5 (6).
9. Truman CJ, Goldberg JF, Ghaemi SN. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 2007; 68 (10): 1472-1479.
10. Henry C, Sorbara F, Lacoste J, Gindre C, Leboyer M. Antidepressant-induced mania in bipolar patients: Identification of risk factors. J Clin Psychiatry 2001; 62 (4): 249-255.
11. Binder MR. Mind-brain dynamics in the pathophysiology of psychiatric disorders. AJPN 2022; 10 (2): 48-62.
12. Krystal AD. Antidepressant and antipsychotic drugs. Sleep Med Clin 2010; 5 (4): 571-589.
13. Gittelman JX, Perke DJ, Portfors CV. Dopamine modulates auditory responses in the inferior colliculus in a heterogeneous manner. J Assoc Res Otolaryngol 2013; 14 (5): 719- 29.
14. Loscher W, Schmidt D. Increase of human plasma GABA by sodium valproate. Epilepsia 1980; 21 (6); 611-615.
15. Edwards R, Stephenson U, Flewett T. Clonazepam in acute mania: a double blind trial. Aust N Z J Psychiatry 1991; 25 (2): 238-242.
16. El-Mallakh RS, Huff O. Mood stabilizers and ion regulation. Harv Rev Psychiatry 2001; 9 (1): 23-32.
17. Ramadan E, Basselin M, Rao JS, et al. Lamotrigine blocks NMDA receptor-initiated arachidonic acid signaling in rat brain: implications for its efficacy in bipolar disorder. Int J Neuropsychopharmacol 2012; 15 (7): 931-943.
18. Newport DJ, Carpenter LL, McDonald WM, et al. APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015; 172 (10): 950-966.
19. Pribish A, Wood N, Kalava A. A Review of nonanesthetic uses of ketamine. Anesthesiol Res Pract 2020; 2020.
20. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 2017 Jul 29; 390 (10093): 480-489.
21. Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. N Engl J Med 2019; 381 (10): 903-911.
22. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: A randomized clinical trial. JAMA Psychiatry 2021; 78 (9): 951-959.
23. Lado FA, Moshé SL. How do seizures stop? Epilepsia 2008; 49 (10): 1651-54.
24. Lambrecq V, Villég F, Marchal C, et al. Refractory status epilepticus: electroconvulsive therapy as a possible therapeutic strategy. Seizure 2012; 21 (9): 661-4.
25. Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA. Electroconvulsive therapy for refractory status epilepticus: a case series. Neurocritical Care 2010; 12 (2): 204-210.
26. Salik I, Marwaha R. Electroconvulsive therapy. StatPearls [Internet] 2022. Last updated September 19, 2022.
27. Gersner R, Kravetz E, Feil J, Pell G, Zangen A. Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: Differential outcomes in anesthetized and awake animals. J Neurosci 2011; 31 (20): 7521-7526.
28. García-Medina NE, Miranda MI. Nucleus of the solitary tract chemical stimulation induces extracellular norepinephrine release in the lateral and basolateral amygdala. Brain Stimul 2013; 6 (2): 198-201.
29. Lynch JH. Stellate ganglion block treats posttraumatic stress: An example of precision mental health. Brain Behav 2020; 10 (11): e01807.
30. Parnia S, Spearpoint K, de Vos G, et al. AWARE — AWAreness during Resuscitation — [2] A prospective study. Resuscitation 2014; 85: 1799-1805.
31. Greyson B. After: A doctor explores what near-death experiences reveal about life and beyond. St. Martin's Essentials. New York, NY 2021.
32. Van Lommel P. Consciousness beyond life: The science of the near-death experience. Harper-Collins Publishers. New York, NY 2010.
33. Moody RA. Life after life. Mockingbird Books 1975.
34. Fenwick P, Fenwick E. The art of dying. Continuum Books. New York, NY 2008.
35. Greyson B, Kelly EF, Dunseath WJR. Surge of neurophysiological activity in the dying brain. Proceedings of the National Academy of Sciences 2013; 110 (47) E4405.
36. Parnia S, Post SG, Lee MT, et al. Guidelines and standards for the study of death and recalled experiences of death—a multidisciplinary consensus statement and proposed future

directions. Annals of the New York Academy of Sciences 2022; 1511 (1): 5-21.
37. Cerf M, Thiruvengadam N, Mormann F, et al. On-line, voluntary control of human temporal lobe neurons. Nature 2010; 467: 1104-1108.
38. Penfield W. Epilepsy and surgical therapy. Archives of Neurology and Psychiatry 1936; 36 (3): 449-484.
39. Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sinauer Associates, Inc. 2001.
40. Merker B. Consciousness without a cerebral cortex: A challenge for neuroscience and medicine. Behavioral and Brain Sciences 2007; 30 (1): 63-134.
41. Kawkabani K. Preserved consciousness in the absence of a cerebral cortex, the legal and ethical implications of redefining consciousness and its neural correlates: A case for a subcortical system generating affective consciousness. Neuroscience and Neurobiology Commons, Honors Research Projects 2018; 734.
42. Theyel BB, Llano DA, Sherman SM. The corticothalamocortical circuit drives higher-order cortex in the mouse. Nature Neuroscience 2010; 13: 84-88.
43. Posner JB, Plum F. Contemporary neurology series. 4. Oxford University Press; Oxford; New York: Plum and Posner's Diagnosis of Stupor and Coma 2007; p. xiv.p. 401.
44. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007; 448 (7153): 600-603.
45. Lemaire J-J, Sontheimer A, Pereira B, et al. Deep brain stimulation in five patients with severe disorders of consciousness. Annals of Clinical and Translational Neurology 2018; 5 (11): 1372-1384.
46. DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy vs. medications for depression: Treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008; 9 (10): 788-796.
47. Binder MR. The multi-circuit neuronal hyperexcitability hypothesis of psychiatric disorders. AJCEM 2019; 7 (1): 12-30.
48. Ferreira MAR, O'Donovan MC, Sklar P. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008; 40 (9): 1056-1058.
49. Yuan A, Yi Z, Wang Q, et al. ANK3 as a risk gene for schizophrenia: new data in Han Chinese and meta analysis. Am J Med Genet B Neuropsychiatr Genet 2012; 159B (8): 997-1005.
50. Green EK, Grozeva D, Jones I, et al., Wellcome Trust Case Control Consortium, Holmans, PA, Owen, MJ, O'Donovan, MC, Craddock N. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry 2010; 15 (10): 1016-1022.
51. Lopez AY, Wang X, Xu M, et al. Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. Mol Psychiatry 2017; 22 (10): 1464–1472.
52. Gargus JJ. Ion channel function candidate genes in multigenic neuropsychiatric disease. Biol Psychiatry 2006; (60) 2: 177-185.
53. Liu Y, Blackwood DH, Caesar S, et al. (2011) Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry. 16 (1).
54. Iqbal Z, Vandeweyer G, van der Voet M, et al. (2013) Homozygous and heterozygous disruptions of ANK3: at the crossroads of neurodevelopmental and psychiatric disorders. Human Molecular Genetics. 22: 1960-1970.
55. Subramanian J, Dye L, and Morozov, A. (2013) Rap1 Signaling Prevents L-Type Calcium Channel-Dependent Neurotransmitter Release. Journal of Neuroscience. 33 (17): 7245.
56. Santos M, D'Amico D, Spadoni O, et al. (2013) Hippocampal hyperexcitability underlies enhanced fear memories in TgNTRK3, a panic disorder mouse model. Journal of Neuroscience. 33 (38): 15259-15271.
57. Contractor A, Klyachko VA, and Portera-Cailliau C. (2015) Altered neuronal and circuit excitability in Fragile X syndrome. Neuron. 87 (4): 699-715.
58. O'Brien NL, Way MJ, Kandaswamy R, et al.The functional GRM3 Kozak sequence variant rs148754219 affects the risk of schizophrenia and alcohol dependence as well as bipolar disorder. Psychiatric Genetics2014; 24: 277–278.
59. Schizophrenia Working Group of the Psychiatric Genomics Consortium: Ripke S, Neale BM, and O'Donovan MC. (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature. 511 (7510): 421-427.
60. Freedman R, Coon H, Myles-Worsley M, et al. (1997) Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. PNAS. 94 (2): 587–592.
61. Pizzarelli R and Cherubini E. (2011) Alterations of GABAergic signaling in autism spectrum disorders. Neural Plast. 1011: 157193.
62. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J Neuroscience 2007; 27 (33): 8877-8884.
63. Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One 2012; 7 (2): 1-13. e32508.

64. Rose GM, Diamond DM, Pang K, Dunwiddie TV. Primed burst potentiation: lasting synaptic plasticity invoked by physiologically patterned stimulation. In: Haas HL, Buzsàki G. (eds) Synaptic plasticity in the hippocampus. Springer, Berlin, Heidelberg, 1988.
65. Hargreave E. (2006). The neuroplasticity phenomenon of kindling. http://hargreaves.swong.webfactional.com/kindle.htm. (Accessed 5/19/18).
66. Guha A, Yee CM, Heller W, Miller GA. Alterations in the default mode-salience network circuit provide a potential mechanism supporting negativity bias in depression. Psychophysiology 2012; 58 (12).
67. Binder MR: The neuronal excitability spectrum: A new paradigm in the diagnosis, treatment, and prevention of mental illness and its relation to chronic disease. AJCEM; 2021; 9 (6): 187-203.
68. Henkel AW, Welzel O, Groemer T W, et al. Fluoxetine prevents stimulation-dependent fatigue of synaptic vesicle exocytosis in hippocampal neurons. Journal of Neurochemistry 2010; 114 (3): 697-705.
69. Varvin S. Which patients should avoid psychoanalysis, and which professionals should avoid psychoanalytic training?: A critical evaluation. Scandinavian Psychoanalytic Review 2014; 26 (26): 109-122.
70. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021; 55 (1): 7-117.
71. Binder MR. A pathophysiolgically-based approach to the treatment and prevention of mental illness and its related disorders. AJCEM 2021; 9 (6): 223-232.
72. Shah B, Elsayed OH, El-Mallakh RS. Bipolar disorder: The foundational role of mood stabilizers. Current Psychiatry 2023; 22 (5): 36-41.
73. Weitz E, Hollon SD, Twisk J, et al.Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: an individual patient data meta-analysis. JAMA Psychiatry 2015; 72:1102–1109.
74. Cuijpers P, De Wit L, Weitz E, et al. The combination of psychotherapy and pharmacotherapy in the treatment of adult depression: a comprehensive meta-analysis. J Evid Based Psychother 2015; 15: 147–168.
75. Khedr EM, Elserogy Y, Fawzy M. Effect of psychotropic drugs on cortical excitability of patients with major depressive disorders: A transcranial magnetic stimulation study. Psychiatry Research 2020; 291: 113287.
76. Godlewska BR, Norbury R, Selvaraj S, Cowen PJ, Harmer CJ. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychol Med 2012; 42 (12): 2609-2617.
77. Hett D, Marwaha S. Repetitive transcranial magnetic stimulation in the treatment of bipolar disorder. Ther Adv Psychopharmacol 2020; 18 (10).
78. Marzouk T, Winkelbeiner S, Azizi H, et al. Transcranial magnetic stimulation for positive symptoms in schizophrenia: A systematic review. Neuropsychobiology 2020; 79: 384–396.
79. Binder MR. Neuronal hyperexcitability: The elusive but modifiable instigator of disease. AJCEM 2022; 10 (1): 1-7.
80. Grunze HCR. The effectiveness of anticonvulsants in psychiatric disorders. Dialogues Clin Neurosci. 2008; 10 (1): 77-89.
81. Yizhar O, Fenno LE, Prigge M, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 2011; 477: 171-178.
82. Binder MR. Electrophysiology of seizure disorders may hold key to the pathophysiology of psychiatric disorders. AJCEM 2019; 7 (5): 103-110.
83. Binder MR. Neuronal hyperexcitability: significance, cause, and diversity of clinical expression. AJCEM 2021; 9 (5); 157-167.
84. Binder MR. Suicide: A new hypothesis on the pathogenesis of disease, method of screening, and means of prevention. AJPN 2022; 10 (3): 111-124.
85. Canadian Health Measures Survey: Cycle 2 Data Tables: Table 3 — Average resting heart rate, by age and sex, household population, Canada, 2009 to 2011.
86. Wallis LA, Healy M, Unde MB, Maconochi I. Age related reference ranges for respiration rate and heart rate from 4 to 16 years. Arch Dis Child 2005; 90: 1117-1121.
87. Binder MR. Gabapentin—The popular but controversial anticonvulsant drug may be zeroing in on the pathophysiology of disease. AJCEM 2021; 9 (4): 122-134.
88. Young LT. What is the best treatment for bipolar depression? J Psychiatry Neurosci 2008; 33 (6): 487-488.
89. Lubloy A, Kereszturi JL, Nemeth A, Mihalicza P. Exploring factors of diagnostic delay for patients with bipolar disorder: a population-based cohort study. BMC Psychiatry 2020; 20 (75).
90. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. The Canadian Journal of Psychiatry 2016; 64 (4).
91. Hirschfeld R, Lewis L, Vornik L. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64 (2): 161-174.
92. Campbell D. People with bipolar disorder may wait 13 years for diagnosis. The Guardian 2012;

https://www.theguardian.com/society/2012/jun/27/bipolar-disorder-diagnosis-survey. (Accessed 10/7/18).
93. Latvala A, Kuja-Halkola R, Rick C, et al. Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: A longitudinal population study of more than 1 million men in Sweden. JAMA Psychiatry 2016; 73 (12): 1268-1275.
94. Blom EH, Serlachius E, Chesney MA, Olsson EMG. Adolescent girls with emotional disorders have a lower end-tidal CO2 and increased respiratory rate compared with healthy controls. Psychophysiology 2014; 51 (5): 412-418.
95. Colangelo LA, Yano Y, Jacobs Jr DR, Lloyd-Jones DM. Association of resting heart rate with blood pressure and incident hypertension over 30 years in black and white adults: The CARDIA study. Hypertension 2020; 76 (3): 692-698.
96. Shi Y, Zhou W, Liu S, et al. Resting heart rate and the risk of hypertension and heart failure: a dose-response meta- analysis of prospective studies. J Hypertens 2018; 36 (5): 995-1004.
97. Shen L, Wang Y, Jiang X, et al. Dose-response association of resting heart rate and hypertension in adults: A systematic review and meta-analysis of cohort studies. Medicine (Baltimore) 2020; 99 (10): e19401.
98. Dalal J, Dasbiswas A, Sathyamurthy I, et al. Heart rate in hypertension: Review and expert opinion. International Journal of Hypertension 2019; 2019.
99. Lee DH, de Rezende LFM, Hu FB, Jeon JY, Giovannucci EL. Resting heart rate and risk of type 2 diabetes: a prospective cohort study and meta-analysis. Diabetes Metab Res Rev 2019; 35 (2): e3095.
100. Aune D, o'Hartaigh B, Vatten LJ. Resting heart rate and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of cohort studies. Nutr Metab Cardiovasc Dis 2015; 25 (6): 526-534.
101. Nagaya T, Yoshida H, Takahashi H, Kawai M. Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type-2 diabetes mellitus. Int J Epidemiol 2010; 39 (1): 215-222.
102. Kannel W, Kannel C, Paffenbarger R, Cupples A. Heart rate and cardiovascular mortality: The Framingham study. Am Heart J 1987; 113: 1489-1494.
103. Gillum R, Makuc D, Feldman J. Pulse rate, coronary heart disease, and death: The NHANES I epidemiologic follow-up study. Am Heart J 1991; 121: 172-177.
104. Cooney MT, Vartiainen E, Laatikainen T, et al. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010; 159 (4): 612-619.
105. Khan H, Kunutsor S, Kalogeropoulos AP, et al. Resting heart rate and risk of incident heart failure: three prospective cohort studies and a systematic meta-analysis. J Am Heart Assoc 2015; 4 (1): e001364.
106. Alhalabi L, Singleton MJ, Oseni AO, et al. Relation of higher resting heart rate to risk of cardiovascular versus noncardiovascular death. Am J Cardiol 2017; 119 (7): 1003- 1007.
107. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ 2016; 188 (3): E53-E63.
108. Yu J, Dai L, Zhao Q. Association of cumulative exposure to resting heart rate with risk of stroke in general population: The Kailuan Cohort Study. Journal of Stroke and Cardiovascular Diseases 2017; (26): 11: 2501-2509.
109. Huang Y-Q, Shen G, Huang J-Y, Zhang B, Feng Y-Q. A nonlinear association between resting heart rate and ischemic stroke among community elderly hypertensive patients. Postgrad Med 2020; 132 (2): 215-219.
110. Aune D,Sen A,o'Hartaigh B, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis 2017; 27 (6): 504-517.
111. Anker MS, Ebner N, Hildenbrandt B, et al. Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. European Journal of Heart Failure 2016; 18 (12).
112. Park J, Kim JH, Park Y. Resting heart rate is an independent predictor of advanced colorectal adenoma recurrence. PLoS One 2018; 13 (3): e0193753.
113. Burke SL. Resting heart rate moderates the relationship between neuropsychiatric symptoms, MCI, and Alzheimer's disease. Innov Aging 2019; 3 (suppl 1): S641.
114. Jouven X, Empana J-P, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352: 1951-1958.
115. Binder MR. FLASH syndrome: tapping into the root of chronic illness. AJCEM 2020; 8 (6): 101-109.
116. Binder MR. Psychiatric and functional physical symptoms: the more telling "fifth" vital sign. AJCEM 2021; 9 (6): 233-237.
117. Binder MR. Anticonvulsants: The psychotropic and medically protective drugs of the future. AJCEM 2012; 9 (5): 174-182.
118. Binder MR. Introducing the term "Neuroregulator" in psychiatry. AJCEM 2019; 7 (3): 66-70.

119. Binder MR. Focused neuroregulation in the treatment and prevention of mental and physical illness. AJCEM 2022; 10 (2): 49-58.
120. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science 14; 346 (6213).
121. Binder MR. Exploring the potential of preventing human disease by genetically altering the excitability of the neurological system. Am J Psychiatry and Neurosci 2023; 11(1): 22-29.

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Neurological Wilson Disease in a Young Brazilian Adult: A Case Report

By Laryssa Garcia de Almeida, Ilana Werneck Augsten, Yan da Silva Raposo, Hiago Antunis Silva, Patrícia Marques Mendes, Igor Pereira Matos de Oliveira & Eduardo Mendonça Werneck da Silva

Abstract- We report a rare case of Wilson's Disease with neurologic features in a 31-year-old man. This disease consists of a disturbance of copper metabolism secondary to a mutation in the gene responsible for encoding the tissue transporter and the enzyme that incorporates the excess element into bile, generating toxic accumulation in the liver, cornea, and central nervous system. According to his wife, the patient had been treated for an unspecified mood disorder. The clinical picture was characterized by depressive mood, anhedonia, and anxiety. He had his first seizure episode on December 3rd, 2021. He progressed with dysarthria, ataxic gait, dystonia of the right-hand flexor muscles, and intermittent urinary incontinence. Marked worsening was observed after the diagnosis of COVID-19 in February 2022. At the clinical evaluation on March 24th, risorius muscle dystonia (risus sardonicus), resting tremor, and Kayser Fleischer rings at slit-lamp examination was also noted.

Keywords: *wilson disease. inborn errors in metal metabolism. dystonia.*

GJMR-A Classification: *NLM: WL 350*

Strictly as per the compliance and regulations of:

Neurological Wilson Disease in a Young Brazilian Adult: A Case Report

Laryssa Garcia de Almeida [α], Ilana Werneck Augsten [σ], Yan da Silva Raposo [ρ], Hiago Antunis Silva [ω], Patrícia Marques Mendes [¥], Igor Pereira Matos de Oliveira [§] & Eduardo Mendonça Werneck da Silva [χ]

Abstract- We report a rare case of Wilson's Disease with neurologic features in a 31-year-old man. This disease consists of a disturbance of copper metabolism secondary to a mutation in the gene responsible for encoding the tissue transporter and the enzyme that incorporates the excess element into bile, generating toxic accumulation in the liver, cornea, and central nervous system. According to his wife, the patient had been treated for an unspecified mood disorder. The clinical picture was characterized by depressive mood, anhedonia, and anxiety. He had his first seizure episode on December 3rd, 2021. He progressed with dysarthria, ataxic gait, dystonia of the right-hand flexor muscles, and intermittent urinary incontinence. Marked worsening was observed after the diagnosis of COVID-19 in February 2022. At the clinical evaluation on March 24th, risorius muscle dystonia (risus sardonicus), resting tremor, and Kayser Fleischer rings at slit-lamp examination was also noted. Cerebrospinal fluid exam without abnormalities. Imaging workup revealed signaled alteration in bilateral putamen, midbrain, and pons. Laboratory tests revealed mild impairment of liver function and abdominal ultrasound with no evident abnormalities. Specific tests confirmed the diagnosis (serum copper and 24-hour urine copper levels elevated and reduced serum ceruloplasmin). This case report represents the importance of a detailed neurological clinical evaluation and the association of findings with imaging and laboratory workup. It is a rare disease whose epidemiology in Brazil lacks data, and complementary tests have reduced specificity. Early diagnosis and treatment have an impact on the neurological prognosis.

Keywords: wilson disease. inborn errors in metal metabolism. dystonia.

I. Introduction

Wilson's Disease (WD) is a metabolic disorder resulting from biallelic mutations in the ATP7B gene on chromosome 13[1,2,3] of autosomal recessive inheritance[3], characterized by the toxic accumulation of this element in the liver, córnea, and central nervous system[4].

Author α ω: Neurology Specialist, Hospital das Clínicas Samuel Libânio, 777 Comendador Jose Garcia St, Pouso Alegre, Minas Gerais, MG 37550-000, BRA.

Author σ: Neurology Specialist, Fellowship in Vascular Neurology, Hospital das Clínicas Samuel Libânio, 777 Comendador Jose Garcia St, Pouso Alegre, Minas Gerais, MG, 37550-000, BRA.

Author ρ ¥ § χ: Neurology Resident, Hospital das Clínicas Samuel Libânio, 777 Comendador Jose Garcia St, Pouso Alegre, Minas Gerais, MG, 37550-000, BRA. e-mail: yanraposo@yahoo.com.br

The incidence of these mutations in newborns was estimated at 1:7,000 in Sardinia, Italy[5] and 1.7:100,000 in the Republic of Ireland[6], in contrast, the prevalence of the disease has been estimated to be between 1:250,000 and 1:300,000 in Sweden and between 1:30,000 and 1:40,000 in other populations[7].

Copper is an essential cofactor for several enzymes[8] and is present in foodstuffs such as seafood, pulses, and nuts[9]. Its metabolism is dependent on the ATP7B gene, which is responsible for encoding ceruloplasmin, and on the ATPase, which incorporates it into the bile and allows its exteriorization with the feces [10,11].

Due to the absence of these mechanisms, copper accumulates in the liver until it spills over into the bloodstream. High levels of cupremia cause disruption of the blood-brain barrier and deposition with a cytotoxic effect in the striatum, globus pallidus, locus coeruleus, substantia nigra, and cerebral cortex [4,12].

II. Case Report

A 31-year-old male, mixed race, bricklayer, residing in Paraisópolis, Minas Gerais State, Brazil. History of alcoholism and drug use. Diagnosis of previous unspecified mood disorder and using Fluoxetine 40mg/day. No other relevant environmental exposures were reported. Report of a male adult family member diagnosed with liver failure of unknown etiology.

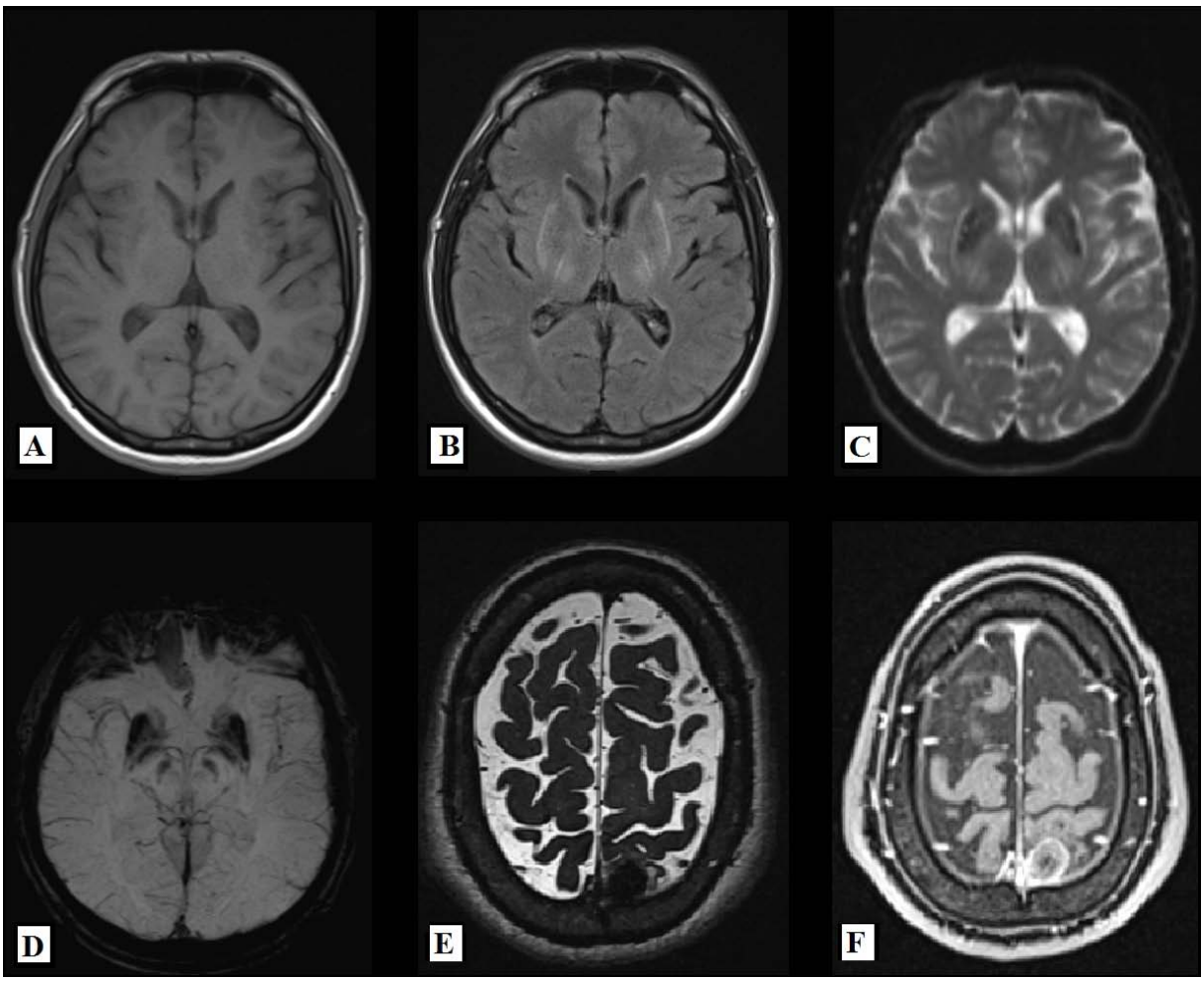
Magnetic Resonance Imaging (MRI) of the brain on December 1st, 2021, showed involvement of the putamen, associated with hemosiderin residue, and crus posterius bilaterally, in addition to the midbrain and pons, without restriction to diffusion (images 1A-1D), and an extra-axial parietal left paramedian contrast-enhanced lesion suggestive of meningioma (images 1E-1F). On December 3rd, 2021, the patient suffered the first generalized clonic tonic seizure while sleeping, and in a follow-up visit on December 21st, he started to use Levetiracetam orally.

He was diagnosed with Covid 19 on February 3rd, 2022, with a mild evolution without the need for ventilatory support or complications. The wife noted that the development of the disease was accentuated after the infection. From February 9th, he appeared to have speech and gait disturbance, difficulty mobilizing the right hand, and urinary incontinence.

On February 16th, he attended the consultation with the responsible physician who, associated the symptoms with the anticonvulsant and switched to Phenytoin 100mg twice a day and associated Dexamethasone orally. It evolved five days later with intermittent hiccups and prostration that lasted approximately three days.

Cerebrospinal fluid (CSF) collected On March 21st revealed a cell count of 0 unit; glucose 89 mg/dL, lactate 15.7 mg/dL, gram without staining bactéria, and CSF culture without bacterial growth.

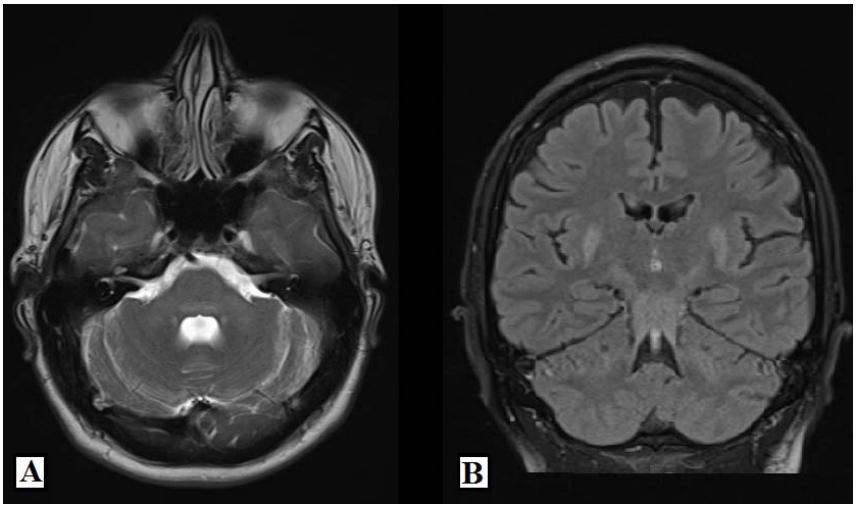
He was hospitalized on March 24th for social reasons to collect WD screening tests. The patient presented to the neurological examination with regular general condition, good spatial orientation, alertness, Glasgow Coma Scale 15, hypomimia, cranial nerve pairs exam without abnormalities, isochoric pupils, normal extrinsic ocular



motricity, risus sardonicus, deep tendon reflexes 2/2, muscle strength 5/5 in all testable upper and lower limb muscle groups, somaesthesia, right-hand flexor dystonia, and ataxic gait. Upon slit lamp examination, the presence of Kayser-Fleischer rings was noted.

Laboratory workup of March 24th revealed aminotransferase (AST) 37 mg/dL, alanine aminotransferase (ALT) 35 mg/dL, total bilirubin test 1,00 mg/dL, albumin test 3,7 mg/dL, international normalized ratio (INR) 1,17, and platelets $88x10^9$ /L. Tests for disorders of Copper metabolism of the same date revealed total serum copper 24,6 mg/dL (reference range (RR) 70mg/dL-150mg/dL), serum ceruloplasmin 7,0 mg/dL (RR 20mg/dL-60mg/dL) and, finally, 24-hours urine copper test 187,4 mg/dL (RR 70mg/dL-150mg/dL). Child-Pugh, Fibrosis-4, and APRI scores were, respectively, 5 points (Child Class A - least severe liver disease); 1,99 (undetermined), and 1,11 (significant fibrosis most likely, cirrhosis undetermined). Abdominal ultrasound exam of April 8th, 2022, indicates chronic liver disease with signs of portal hypertension, splenomegaly, and moderate ascites. Electroneuromyography of March 14th, 2022, was absent abnormalities.

During outpatient follow-up, a new MRI of the brain was requested on April 1st, 2022, which denoted better characterization of foci of signal alteration in cerebellar peduncles (images 2).



On June 2022, he had moderate dysarthria, hypomimia, right-hand flexor dystonia, tetraparesis, bradykinesia, and postural instability, but without rigid or resting tremors.

The specific treatment was started on May 2022 with pyridoxine chlorhydrate 50 mg daily and zinc sulfate heptahydrate 4 mg/mL 15mL three times a day orally. Due to the cost of the drug, the patient delayed starting penicillamine.

III. Discussion

Incipient neurological symptoms are subtle and nonspecific, such as difficulty concentrating and motor coordination and handwriting changes (for example, micrograph) [13-19] and begin on average between 20 and 40 years [20-22]. As it progresses, more prominent symptoms appear, whose order of incidence is dysarthria (57.6%), dystonia (42.4%), abnormal gait (37.8%), tremor (36.2%), parkinsonism (17.3%), choreoathetosis (15.3%) and convulsion (4.7%) [16,17]. Neurological impairment occurs about a decade after liver failure and, therefore, signs of advanced disease [23]. Cognitive impairment is considered rare and was reported by Machado, Chien, Deguti, et al. (2006)[16] in 4.2% of cases.

Given the heterogeneity of clinical manifestations, the neurological phenotype of WD can be grouped for didactic purposes into dystonic, pseudosclerotic, parkinsonian, and hyperkinetic subtypes [4]. The patient discussed in this study had a predominance of the dystonic subtype manifested by multifocal dystonia affecting both the risorius muscle (sardonic laughter) and the flexor muscles of the right hand fingers. As reported by Lorincz (2010) [24], bilateral putaminal lesions were found on an MRI of the brain.

Dysarthria can result from any condition that damages the motor control structures necessary for speech production, such as cranial nerves IX, X, XII, cerebellum, and basal ganglia [12]. In this case, it was noted evident bilateral impairment of the basal ganglia.

Seizures are not uncommon and are reported variably in 4.7% [16,17] to 14.5% [25] of WD cases. The patient in question presented, at the initial manifestation, a single episode of generalized tonic-clonic seizure without recurrence.

We also detected the presence of brownish Kayser Fleischer rings, more evident in the lower region of the iris bilaterally. Such a semiological sign is due to copper deposition in the Descemet's membrane of the cornea [26] and is present in approximately 100% of neuropsychiatric WD cases [10].

Psychiatric symptoms are reported by about 30% to 60% of individuals affected by WD [26]. In this case, the disorder for which the patient had been using Fluoxetine was not specified. However, the familiar states that at the time of initiation of therapy, he had a depressive mood, anhedonia, and anxiety.

It is possible that such symptoms were already an incipient manifestation of central nervous system involvement.

Cognitive impairment is initially mild and recognized only by family members. It is categorized into frontal lobe syndrome, which involves impulsivity, promiscuity, apathy, hypotenacity, impaired social judgment, planning dysfunction, and emotional lability, and subcortical dementia characterized by slowed thinking amnesia, and executive dysfunction, but without aphasia, apraxia, or agnosia [10]. In this case, it was impossible to attribute a clinical syndrome related to the metabolic disorder, given the history of alcoholism and use of narcotics.

IV. Conclusion

This case report represents the importance of a detailed neurological clinical evaluation and the association of findings with Imaging and laboratory workup. It is a rare disease whose epidemiology in Brazil lacks data, and complementary tests have reduced specificity.

Disclosure statement

No potential conflict of interest was reported by the authors.

References Références Referencias

1. Bull PC, Tomás GR, Rommens JM, Forbes JR, Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat. Genet. 1993; 5: 327-337.
2. Tanzi RE, Petrukhin K, Chernov E, Pellequer JL, Wasco W, Ross B, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat. Genet. 1993; 5: 344–350.
3. Faoucher M, Caroline D. The psychopharmacology of Wilson disease and other metabolic disorders. Handbook of clinical neurology. 2019; 165: 191-205.
4. Hedera P. Wilson's disease: A master of disguise. Parkinsonism & Related Disorders. 2019; 59: 140-145.
5. Loudianos G, Dessi V, Lovicu M, Angius A, Figus A, Lilliu F, et al., Molecular characterization of Wilson disease in the Sardinian population–evidence of a founder effect. Hum. Mutat. 1999; 14: 294–303.
6. Reilly M, Daly L, Hutchinson M. An epidemiological study of Wilson's disease in the Republic of Ireland. Journal of Neurology, Neurosurgery & Psychiatry. 1993; 56(3): 298–300.
7. Olsson C, Waldenström E, Westermark K, Landegre U, Syvanen AC. Determination of the frequencies of ten allelic variants of the Wilson disease gene (ATP7B), in pooled DNA samples. Eur. J. Hum. Genet. 2000; 8: 933–938.
8. Lopes LAL, Souza SEM, Filho VMA, Borges MAF. Mielopathy related to copper deficiency after bariatric surgery: case report Mielopatia relacionada à deficiência de cobre após cirurgia bariátrica: relato de caso. Brazilian Journal of Health Review. 2021; 4(6): 27188-94.
9. Roberts EA, Schilsky ML. American association for study of liver diseases (AASLD). Diagnosis and treatment of Wilson's disease: an update. Hepatology. 2008; 47: 2089–2111.
10. Lorincz MT. Wilson disease and related copper disorders. Handbook of Clinical Neurology. 2018; 147: 279–292.
11. Tussolini IGA, Tussolini GR, Tussolini JF, Pontes LS, Junior MTR, Silva, PD. Doença de Menkes: relato de um caso raro na Amazônia. *Brazilian Journal of Health Review*. 2023; *6*(1): 4016-26.
12. Ortiz JF, Cox AM, Tambo W, Eskander N, Wirth M, Valdez M, et al. Neurological Manifestations of Wilson's Disease: Pathophysiology and Localization of Each Component. Cureus. 2020; 12(11):e11509.
13. Walshe JM. Wilson's disease. The presenting symptoms. Arch. Dis. Child. 1962; 37: 253–256.
14. Saito T. Presenting symptoms and natural history of Wilson disease. Eur. J. Pediatr. 1987; 146: 261–265.
15. Oder W, Grimm G, Kollegger H, Ferenci P, Schneider B, Deecke L. Neurological and neuropsychiatric spectrum of Wilson's disease: a prospective study of 45 cases. J. Neurol. 1991; 238: 281–287.
16. Machado A, Chien HF, Deguti MM, Cançado E, Azevedo RS, Scaff M, et al. Neurological manifestations in Wilson's disease: report of 119 cases. Mov. Disord. 2006; 21: 2192–2196.
17. Burke JF, Dayalu P, Nan B, Askari F, Brewer GJ, Lorincz MT. Prognostic significance of neurologic examination findings in Wilson disease. Park. Relat. Disord. 2011; 17: 551–556.
18. Członkowska A, Litwin T, Dzieżyc K, Karliński M, Bring J, Bjartmar C. Characteristics of a newly diagnosed Polish cohort of patients with neurological manifestations of Wilson disease evaluated with the Unified Wilson's Disease Rating Scale. BMC Neurol. 2018; 18: 34.
19. Rubinstein SS, Young AB, Kluin K, Hill G, Aisen AM, Gabrielsen T, et al. Clinical assessment of 31 patients with Wilson's disease. Correlations with structural changes on magnetic resonance imaging. Arch. Neurol. 1987; 44: 365–370.
20. Cauza E, Dobersberger TM, Polli C, Kaserer K, Kramer L, Ferenci P. Screening for Wilson's disease in patients with liver diseases by serum ceruloplasmin. J. Hepatol. 1997; 27: 358–362.
21. Xu X, Pin S, Gathinji M, Fuchs R, Harris ZL. Aceruloplasminemia: an inherited neuro-degenerative disease with impairment of iron homeostasis. Ann. N. Y. Acad. Sci. 2004; 1012: 299–305.
22. Tümer Z. An overview and update of ATP7A mutations leading to Menkes disease and occipital horn syndrome. Hum. Mutat. 2013; 34: 417–429.
23. Ferenci P. Pathophysiology and clinical features of Wilson disease. Metabolic brain disease. 2004; 19: 229-39.
24. Lorincz MT. Neurologic Wilson's disease. Ann N Y Acad Sci; 2010: 1184: 173–187.
25. Prashanth LK, Sinha S, Taly AB, Mahadevan A, Vasudev MK, Shankar SK. Spectrum of epilepsy in Wilson's disease with electroencephalographic, MR imaging and pathological correlates. J Neurol Sci. 2010; 291: 44–51.
26. Stremmel W, Merle U, Weiskirchen R. Clinical features of Wilson disease. Annals of Translational Medicine. 2019; 7(2): 61.

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A Case of GM 1 Gangliosidosis Type 2 Mimicking Zellweger Syndrome

By Narendranath Reddy Ganampet, Poornima Jaiswal Charpuria,
Praver Chandan Chemudupati Parven, Shresta Mary K,
Dirgha Upendrabhai Patel & Smaran Kasireddy

Abstract- Juvenile GM1-gangliosidosis, also known as type II or juvenile GM1-gangliosidosis, is an autosomal recessive lysosomal storage disorder that clinically differs from infantile GM1-gangliosidosis in the absence of the characteristic cherry-red patch and hepatosplenomegaly. The disease is characterized by mild skeletal abnormalities and slowly progressing neurodegeneration. Due to the late age of onset and unusual presentation, diagnostic confusion with other ataxic and purely neurological disorders is common. There are currently 3–4 recognized types of GM1-gangliosidosis, with type I being the most prevalent phenotype with an average onset age of 6 months. Several subtypes of GM1-gangliosidosis are caused by mutations in the GLB1 gene, but the location and type of deleterious mutations have a direct impact on the severity of the disease and the age at which it manifests.

Keywords: *GM1 gangliosidosis; lysosomal storage disease; beta-galactosidase.*

GJMR-A Classification: *NLM: WL 17, D009190 ACM: I.2.1*

A Case of GM 1 Gangliosidosis Type 2 Mimicking Zellweger Syndrome

Narendranath Reddy Ganampet [α], Poornima Jaiswal Charpuria [σ], Praver Chandan Chemudupati Parven [ρ], Shresta Mary K [ω], Dirgha Upendrabhai Patel [¥] & Smaran Kasireddy [§]

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Keywords: GM1 gangliosidosis; lysosomal storage disease; beta-galactosidase.

I. Introduction

For cells to function efficiently, the processes of glycoconjugate production and degradation need to be carefully controlled. Glycoconjugates are essential for the majority of biological processes. -galactosidase, also known as GAL, is a lysosomal hydrolase that is responsible for the degradation of a wide variety of glycoconjugates. This is accomplished by hydrolyzing the non-reducing end of glycan moieties. This enzyme's primary role is to delink galactose residues from one another. According to research [1, 2], GM1 ganglioside and its asialo derivative GA1 have a tendency to concentrate in the lysosomes that are present in brain tissue. The clinical signs of the illness are caused by neurodegenerative pathways in the brain that are triggered when there is an excess of ganglioside—Galactosidase substrate. The accumulation of GM1 gangliosides in microglial cells of the central nervous system has been demonstrated to result in greater activation and infiltration of inflammatory cells into these cells, according to studies conducted using animal models. Previous research [3] has shown that inflammation seems to have a key role in both the etiology of the disorder as well as the neurological symptoms of the condition. It is believed that GM1 gangliosidosis affects between 1 in 100,000 and 200,000 neonates [4]. These numbers are based on estimates from previous studies. Type II GM1 gangliosidosis, sometimes called juvenile or late infantile GM1 gangliosidosis, is distinguished by the slow onset and progression of clinical signs. Ataxia is often the first obvious symptom associated with this subtype, followed by dystonia and spasticity. People who have type II GM 1 gangliosidosis do not have the usual signs of hepatosplenomegaly, cherry red patches, or distinctive facial characteristics. This makes it challenging to make an accurate diagnosis of the condition. People who have this syndrome seem to develop normally in the early stages of the illness. However, symptoms often begin to manifest between the ages of 3 and 5 in those affected by the juvenile form, but they appear sooner in those affected by the late infantile variety. The clinical appearance of GM1 gangliosidosis type II is characterized by diminished neurodevelopmental abilities, including motor and verbal skills. This is one of the disease's defining characteristics. Those who are affected may also have seizures that are difficult to control, which is another potential symptom. Previous research [5] has uncovered conclusions that are comparable to this one. Although the patient had an atypical clinical appearance, it was more suggestive of Zellweger syndrome than anything else. Zellweger syndrome is a hereditary condition that may be identified by the presence of peroxisome deficits. Hypotonia, often known as a loss of muscular tone, and weak or nonexistent vocalizations are two of the hallmarks of this condition, which is frequently brought on by mutations in the PEX gene. Infants affected by this disorder often struggle to feed and may experience the development of seizures at an earlier age.

Author α: Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, India.
Author σ: Osmania Medical College - Hyderabad, India.
Author ρ: Gandhi Medical College, Hyderabad, India.
Author ω: Chalmeda Anand Rao institute of medical sciences, Karimnagar, India.
Author ¥: Baroda Medical College, Vadodara, India.
Corresponding Author §: JJM Medical College, Davangere, India.
e-mail: smaran.psbb@gmail.com

II. Ethical Approval

The patient's mother consented to the publication of this deidentified case report. Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

III. Clinical Summary

We describe a case of an 8-month-old baby who was identified as having Type 2 GM-1 Gangliosidosis. After an uneventful first pregnancy, the patient was the third child of the consanguineous, healthy parents. His older sister appears to be completely normal. The patient had an inguinal hernia, which was discovered during the prenatal ultrasound screening. The patient was once sent to the hospital at the age of 2 months for a hernia operation, during which it was discovered that he had breathing problems. However, with proper measures the surgical procedure was conducted and the patient was shifted to the ICU for a day. Gradually the patient became better with continuous nebulization and was finally discharged. At 8 months of age, the patient's parents again reported to the hospital with complaints of difficulty in breathing, periorbital puffiness and fever since 3 days in the child. The mother also noticed that the baby was having difficulty in sucking milk and drinking and used to intermittently stop feeding. An increased incident of sweating was observed in the baby while feeding. Upon taking the history, it was revealed that the baby had a running nose and history of cough at 5 months of age for which he had taken treatment from a pulmonologist. Upon examination, it was found that the infant showed clinical signs of pneumonia, bilateral hydrocele, macrocephaly, dolichocephaly, frontal bossing, hypotonia, rickets, and global developmental delay *[FIGURE 1]* A Zellweger syndrome suspect was identified.

Morphological features of the face and exhibition of hypotonia

The infant was found to have bilateral enlarged kidneys and hepatosplenomegaly upon abdominal examination. There was also a slight ascites present. The brain's magnetic resonance imaging (MRI) revealed widespread corpus callosum thinning, moderately dilated bilateral occipital horns, and insufficient myelination in parieto-occipital white matter. The infant screened positive for rickets, bicytopenia, and severe anaemia in the lab. He had stage 2 hypotension, a well-functioning dilated left ventricle, mild pericardial effusion, and bilateral pleural effusion, according to his echocardiography. The patient's symptoms were controlled while a confirmative diagnosis was made through gene testing.

A homozygous single base pair deletion in exon 10 of the GLB1 gene, which causes a frameshift and an early truncation of the protein 11 amino acids downstream to codon 327, was discovered, according to the gene report. Another homozygous 2-base pair deletion in exon 11 of the CEP41 gene was discovered

[FIGURE 2], which causes a frameshift and an early truncation of the protein downstream of codon 346. The mutation in the CEP41 gene may be significant, but the gene testing reports classify it as a variant of unknown importance because it is placed in the gene's last exon and its impact on protein alteration cannot be predicted. There was a dearth of literature supporting this variety.

Gene transcripts showing various variations

Gene# (Transcript)	Location	Variant	Zygosity
***GLB1* (-)** (ENST00000307363.10)	Exon 10	c.979del **(p.Gln327SerfsTer11)**	Homozygous

ADDITIONAL FINDINGS: VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

Gene# (Transcript)	Location	Variant	Zygosity
***CEP41* (-)** (ENST00000675138.1)	Exon 11	c.1036_1037del **(p.Asn346LeufsTer?)**	Homozygous

Gene Transcript	Location	Variation	Zygosity
GLB1(-) (ENST00000030763.10)	Exon 10	c.979del (p.Gln327SerfsTer11)	Homozygous

Gene Transcript	Location	Variation	Zygosity
CEP41(-) (ENST00000675138.1)	Exon 11	C.1036_1037del (p.Asn346LeufsTer)	Homozygous

IV. Discussion

In this particular instance, there are a few aspects that should be brought to the forefront. The diagnosis of GM-1 Gangliosidosis Type 2 was arrived at after taking into account the clinical phenotype in addition to specific laboratory and genetic abnormalities. The condition known as juvenile GM1 gangliosidosis, which is passed down in an autosomal recessive manner and results in neurological regression in those who are affected by it, was just described. Patients affected by GM1 gangliosidosis type I begin to display clinical symptoms within the first month of their lives. People who have GM1 gangliosidosis type II continue to reach their typical neurodevelopmental milestones (juvenile form) until late infancy (late infantile form) or late childhood. This is the case even in the juvenile form. Because of this, treatment options for diseases with a later onset, such as enzyme replacement therapy, cell therapy, and bone marrow transplantation, can be more successful if molecular diagnosis is performed early on in pre-symptomatic individuals who have a positive family history. There is currently no simple biochemical test available that can be used for carrier screening in high risk people and their families [6]. It has been reported in the past that patients with type II diabetes have an enzyme activity level that is affected less severely [7]. The GM1 gangliosidosis type II and the discovered mutation in the GLB1 gene appear to be completely correlated with one another, with 100 percent phenotypic plasticity in individuals who are homozygous for the mutation. In spite of the fact that heterozygous carriers for this mutation do not appear to be suffering from any symptoms of illness, there is a risk that they will pass on the deleterious mutation to their offspring. As a consequence of this, people who have had childhood ataxia and the relatives of patients who are already well-known should get a GLB1 genetic test before getting married consanguineously. Consanguineous marriage, a family history of deaths with similar symptoms, increasing ataxia, and neurodevelopmental regression are all factors that assist medical professionals in narrowing down the list of possible alternative diagnoses and advising patients on the most appropriate genetic tests.

V. Conclusion

Juvenile GM1 gangliosidosis type II was shown to have an autosomal recessive variant caused by a missense mutation in the GLB1 gene in our patient. The

mutation is a rare previously reported pathologic mutation along with the mutation in CEP41 gene. The significance of the later gene's mutation in the illness of the patient is yet to be discovered.

Our findings support a connection between juvenile gangliosiodis type II patients' ataxia and neurodegeneration and the GLB1 gene mutation.

References Références Referencias

1. Caciotti, A., Garman, S. C., Rivera-Colon, Y., Procopio, E., Catarzi, S., Ferri, L., et al. (2011). GM1 gangliosidosis and Morquio B disease: an update on genetic alterations and clinical findings. *Biochim. Biophys. Acta* 1812, 782–790. doi: 10.1016/j.bbadis.2011.03.018
2. Jarnes Utz, J. R., Kim, S., King, K., Ziegler, R., Schema, L., Redtree, E. S., et al. (2017). Infantile gangliosidoses: mapping a timeline of clinical changes. *Mol. Genet. Metab.* 121, 170–179. doi: 10.1016/j.ymgme.2017.04.011
3. Jeyakumar M, Thomas R, Elliot-Smith E, Smith D, Van Der Spoel A, d'Azzo A, Perry VH, Butters T, Dwek R, Platt F. Central nervous system inflammation is a hallmark of pathogenesis in mouse models of GM1 and GM2 gangliosidosis. *Brain.* 2003; 126(4): 974–87. doi: 10.1093/brain/awg089.
4. Armstrong-Javors A, Chu CJ. Child neurology: Exaggerated dermal melanocytosis in a hypotonic infant: a harbinger of GM1 gangliosidosis. *Neurology.* 2014; 83 (17): e166–8. doi: 10.1212/WNL.0000000000000912.
5. Wolfe LS, Senior RG, Kin NNY. The structures of oligosaccharides accumulating in the liver of GM1-gangliosidosis, type I. *J Biol Chem.* 1974; 249(6): 1828–38.
6. Acosta W, Martin R, Radin DN, Cramer CL. High-throughput imaging method for direct assessment of GM1 ganglioside levels in mammalian cells. *Data Brief.* 2016; 6: 1016–22. doi: 10.1016/j.dib.2016.01.027.
7. Yoshida K, Oshima A, Shimmoto M, Fukuhara Y, Sakuraba H, Yanagisawa N, Suzuki Y. Human beta-galactosidase gene mutations in GM1-gangliosidosis: a common mutation among Japanese adult/chronic cases. *Am J Hum Genet.* 1991; 49(2): 435–42.

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A Precision Medicine Approach to the Treatment of Psychiatric Disorders

By Michael Raymond Binder, M.D.

Abstract- Due to a lack of clarity about the pathophysiology of psychiatric disorders, short and long-term treatment outcomes continue to be very inconsistent, and the prescribing of multiple medications that can have unpredictable, conflicting, and sometimes paradoxical effects continues to be more the rule than the exception in modern psychiatric practice. Dosing is also an issue, as standard doses of psychotropic drugs are often too high, thus causing some patients to incur unnecessary side effects, which in turn can lead to poor compliance or even discontinuation of treatment. Worse yet, these negative outcomes can cause disappointed patients to dissuade other would-be patients from seeking treatment. Recognizing these concerns and the fact that most persons with mental illness never seek treatment to begin with, the need for greater precision and fewer side effects in the prescribing of psychotropic drugs cannot be overstated.

Keywords: *neuronal hyperexcitability, psychotropic drugs, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, medication side effects, mental health crisis, preventive medicine.*

GJMR-A Classification: *UDC: 159.9*

Strictly as per the compliance and regulations of:

A Precision Medicine Approach to the Treatment of Psychiatric Disorders

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Abstract- Due to a lack of clarity about the pathophysiology of psychiatric disorders, short and long-term treatment outcomes continue to be very inconsistent, and the prescribing of multiple medications that can have unpredictable, conflicting, and sometimes paradoxical effects continues to be more the rule than the exception in modern psychiatric practice. Dosing is also an issue, as standard doses of psychotropic drugs are often too high, thus causing some patients to incur unnecessary side effects, which in turn can lead to poor compliance or even discontinuation of treatment. Worse yet, these negative outcomes can cause disappointed patients to dissuade other would-be patients from seeking treatment. Recognizing these concerns and the fact that most persons with mental illness never seek treatment to begin with, the need for greater precision and fewer side effects in the prescribing of psychotropic drugs cannot be overstated. Based on an emerging hypothesis on the pathophysiology of psychiatric disorders, this article will discuss a promising new approach to psychopharmacotherapy that has the potential to simplify drug selection, reduce dosing requirements, and minimize side effects. By targeting the core physiological abnormality in psychiatric disorders, the use of medications that have unpredictable, conflicting, and sometimes paradoxical effects can be minimized, and the lowest doses of the most appropriate drugs can be used to achieve faster, more consistent, and more enduring therapeutic effects in a group of disorders that are now considered to be a public health crisis.

Keywords: neuronal hyperexcitability, psychotropic drugs, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, medication side effects, mental health crisis, preventive medicine.

I. Introduction

Due to a lack of clarity about the pathophysiology of psychiatric disorders, treatment outcomes in psychiatry continue to be very inconsistent [1, 2], and the prescribing of multiple medications that can have unpredictable, conflicting, and sometimes paradoxical effects has become more the rule than the exception [3]. Many patients are also confused about their diagnosis and how it relates to their treatment. Of equal concern is the fact that most patients who need psychiatric care fail to seek care. Based on data from the Mental Health Million project [4], which polled the English-speaking population of 10 countries, 58% of those questioned did not seek help for clinically apparent mental health issues. In the United Kingdom, only 50% sought help, and in the United States, only 45% sought help. The possible reasons for these low numbers include limited access to care, insufficient financial resources, failure to recognize one's need for care, lack of confidence in the benefits of care, the stigma of mental illness, and fear of taking psychotropic drugs [5]. This last reason—fear of taking psychotropic drugs—usually centers around concerns that such drugs could cause a change in personality, a worsening of symptoms, debilitating side effects, or social stigma. Therefore, with all of these concerns looming in the mind of the patient, it is incumbent upon clinicians to clearly explain what pathological process they are treating when they prescribe psychotropic medication. Clinicians should also strive to minimize both the number of medications and the side effects of those medications. However, the problem that clinicians face is that the underlying cause of most psychiatric disorders remains unclear. Consequently, they can neither visualize what they are treating nor can they properly explain to patients what they are treating.

This article will discuss a promising new approach to psychopharmacotherapy that, based on new insights into the pathophysiology of psychiatric disorders, has the potential to guide better patient education about treatment, improve the quality of treatment, and minimize the side effects of treatment. By targeting the core physiological abnormality in psychiatric disorders, the use of drugs that have unpredictable, conflicting, and sometimes paradoxical effects can be replaced by drugs that, being directed squarely at the biological target, can achieve faster, more consistent, and more enduring therapeutic effects.

II. Background of Psychotropic Drug Selection

Historically and still today, the medical treatment of psychiatric disorders is primarily symptom-based rather than pathology-based. This is the unfortunate consequence of a lack of consensus on the pathophysiology of psychiatric disorders. Although many behavioral health experts believe that most of the common psychiatric disorders, such as generalized anxiety disorder, major depressive disorder, bipolar disorder, and schizophrenia, are rooted in a shared biological abnormality [6-9], there are still many who

Author: Adult and Adolescent Psychiatry, 5 Revere Drive, Suite 200, Northbrook, USA. e-mail: mbinder@drmichaelbinder.com

believe that each psychiatric syndrome has its own unique biological underpinnings [10]. The need to better understand these disorders has become imperative, as the effectiveness of treatment is lagging far behind the escalating mental health crisis. Thus far, the only psychiatric disorder for which there has been a consensus opinion is clinical depression, for which the monoamine hypothesis has guided the use of antidepressants for more than fifty years [11]. Over the past decade, however, even this hypothesis has been called into question because of its failure to explain several important observations. First, it fails to explain how antidepressants can be effective in the treatment of psychiatric disorders other than clinical depression [12]; second, it fails to explain why a depletion of serotonin precursors does not produce depression symptoms in healthy subjects [13]; third, it fails to explain why antidepressants can sometimes cause a paradoxical worsening or cycling of symptoms [14-18]; and fourth, it fails to explain how the putative abnormalities in monoamine transmission actually translate into depressive symptomatology [19].

However, an emerging hypothesis offers answers to these questions and supersedes the monoamine hypothesis by providing the first neuropsychiatric explanation for a wide range of psychiatric disorders and related clinical observations. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis, psychiatric symptoms, irrespective of their symptom-based diagnosis, are caused by pathological hyperactivity in the associated neuronal circuits [20]. Thus, for example, pathological hyperactivity in anxiety circuits causes elevated and persistent feelings of anxiety; pathological hyperactivity in depressive circuits causes elevated and persistent feelings of depression; and pathological hyperactivity in cognitive circuits causes racing thoughts and obsessive thinking [20]. The most common cause of this hyperactivity is thought to be cognitive-emotional stress, as tension in the mind, like stones being thrown at a beehive, has an agitating effect on the brain. According to the MCNH hypothesis, this agitating effect is abnormally amplified when the neurons of the brain, like irritable bees, are inherently hyperexcitable [19]. This would not only explain many observations that the monoamine hypothesis does not [11, 21], but it would also incorporate the effects of brain structure [22], brain physiology [19, 20], brain circuitry [20, 23], and mind-brain dynamics [19] to explain virtually every phenomenon that has been observed clinically in psychology and psychiatry [22-27]. It would also explain why there is so much overlap between symptom-based psychiatric diagnoses [22], and why the same medications can often be used to treat multiple psychiatric syndromes [28, 29].

III. Toward a Pathology-based Approach to Treatment

What the MCNH hypothesis suggests is that a wide range of psychiatric disorders, including generalized anxiety disorder, major depressive disorder, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, and schizophrenia, could be treated by simply reducing the excitability of the neurological system. Although the use of anticonvulsants had traditionally been relegated to the treatment of bipolar disorder [30, 31], the added ability of these drugs to treat a wide range of psychiatric disorders is illustrated by three significant advances in psychiatry: 1) the establishment of bipolar spectrum disorders as a dimensional diagnosis [7, 8]; 2) the recognition that anticonvulsants are the drugs of choice for all disorders in the bipolar spectrum [32]; and 3) the rapid antidepressant effects of ketamine [33, 34] and zuranolone [35-37], both of which have potent brain-calming effects. Still, that raises the question of why it has taken so long to recognize the broad applicability of anticonvulsants.

The answer lies in the flood of excitement that was created when the antidepressant effect was serendipitously discovered in the 1950s. An Associated Press release from Staten Island's Seaview Hospital, where the mood-elevating effect of anti-tuberculin drugs was first recognized, captured a telling scene: patients dancing in celebratory mood [38]. Some of the patients, who were still in quarantine for tuberculosis, were feeling so good emotionally that they wanted to leave the hospital against medical advice. In other words, the antidepressant effect of isoniazid was not just normalizing mood; it was elevating mood to the point of affecting judgement. Nonetheless, the impressiveness of the effect and subsequent acceptance of the monoamine hypothesis as a neurochemical explanation for the effect caused it to be heralded as a medical breakthrough. Subsequently, clinicians became strongly entrained to prescribe antidepressants for almost any patient who presented with depressive symptomatology.

However, consistent with the idea that antidepressants were causing a subtle, mood-related distortion of judgment, their use was also found to increase the risk of switching from depression to mania in some patients [15-18]. Based on evidence that this risk was greatest in patients with bipolar disorder [14-18], concerted efforts were made to distinguish bipolar disorder from unipolar depression [7, 39-41]. The problem is that these two disorders can be indistinguishable, at least until the first manic phase of bipolar disorder occurs. Even then, the diagnosis can be delayed because mania itself often evades detection. The difficulty of making an accurate diagnosis is illustrated by the fact that the average patient with bipolar disorder is misdiagnosed with unipolar

depression for years or even decades before the correct diagnosis is made [42-44]. The risk of misdiagnosis is even greater for those with milder forms of bipolar disorder, such as bipolar II disorder, cyclothymic disorder, and cyclic depression, and it is conceivable that many such patients are never correctly diagnosed. This is a matter of grave concern because, in addition to causing bipolar switching, antidepressants can worsen the course of disorders in the spectrum, sometimes with disastrous consequences [14, 40].

Fortuitously, the challenge of distinguishing bipolar spectrum disorders from unipolar depression can be circumvented by applying the MCNH hypothesis because the hypothesis is pathology-based rather than symptom-based. Treatment is aimed at reducing the excitability of the neurological system rather than specific symptoms. By addressing the root cause of psychiatric symptoms, all of the symptoms, including symptom-cycling, can be reduced simultaneously. According to the MCNH hypothesis, symptom-cycling is the consequence of aberrant circuit induction, a kind of neurological short-circuiting that occurs when pathologically hyperactive feeder circuits stimulate activity in circuits that would normally be less active [20, 22, 23]. Persons with inherently hyperexcitable neurological systems have a tendency to cycle both because their neuronal circuits have a propensity to become pathologically hyperactive and because their relatively hypoactive receiver circuits are themselves hyperexcitable. Also, because the frequency with which symptoms cycle would depend upon the total number of neuron-to-neuron connections, the MCNH hypothesis would predict that those patients with the most neurons would be the most rapid cyclers, whereas those with the least neurons would be the least rapid cyclers [22]. Patients with an intermediate number of neurons could experience cycles within cycles [22, 45, 46]. It is also possible that some cognitive-emotional states, such as intense grief, could keep the locus of hyperactivity stuck in one specific firing pattern, thus tending to prevent symptoms from cycling [19, 22]. Thus, using the MCNH hypothesis, it would not be the frequency of cycling nor even the presence of cycling that would guide medication selection but, rather, the excitability of the neurological system.

IV. How to Identify the Neuronal Hyperexcitability Trait Independent of Psychiatric Symptomatology

Although the ability to identify the neuronal hyperexcitability trait independent of psychiatric symptomatology had previously been lacking, an explosion of recent studies has identified an association between resting vital-sign measurements and the later development of various psychiatric conditions. In a longitudinal study involving more than one million men in Sweden, Latvala et al. [47] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [48] found that adolescent girls with various emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of chronic medical conditions, including diabetes [49-52], high blood pressure [53-55], cardiovascular disease [56-61], cancer [62-64], dementia [65], and all-cause mortality [62, 66]. The subtle vital-sign elevations with which these disease processes are associated are thought to be the consequence of a tonic elevation in basal neurological activity in persons who inherit the genes for neuronal hyperexcitability [25]. In other words, neuronal hyperexcitability could be at the root of a wide range of chronic medical conditions in addition to various psychiatric conditions. Hypothetically, the reason that psychiatric symptoms tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and systems of the body [67]. The physical consequences tend to be delayed because they express the gradual erosive effects of neuronal hyperexcitability, which can take years or even decades to occur [25, 68, 69]. The fundamental mechanism by which neuronal hyperexcitability is thought to drive these erosive effects is the same as that by which it is thought to drive the elevated vital signs: hyper-activation of the sympathetic nervous system [25]. Chronic sympathetic dominance, which maintains the body in a catabolic state, accelerates the aging process and increases one's vulnerability to every disease process that chronic stress can drive. It has been estimated that, in the absence of any significant cardiorespiratory disease, confounding medications, or substances of abuse, an RHR above 75 beats/min or an RRR above 15 breaths/min is indicative of the neuronal hyperexcitability trait [22, 25]. In addition to providing an objective method of identifying the neuronal hyperexcitability trait, the association between resting vital signs and chronic illness could help explain why the lifespan of persons with severe mental illness tends to be so much shorter than the general population [25, 68, 69]. It also suggests that, in addition to reducing psychiatric symptoms, reducing the excitability of the neurological system could help postpone or even prevent the development of a wide range of chronic diseases. This idea is supported by the anecdotal observation that effective treatment with anticonvulsants frequently lowers resting heart and respiratory rate measurements quite significantly.

In addition to simplifying diagnostics and guiding treatment, the MCNH hypothesis predicts that the vast majority of persons who struggle with

psychiatric symptoms have relatively high levels of neuronal excitability. This follows from the fact relatively minor stressors, which would be sufficient to precipitate psychiatric symptoms in persons with higher levels of neuronal excitability, are experienced much more often than the unusually high stressors that would be necessary to precipitate psychiatric symptoms in persons with lower levels of neuronal excitability [70]. Persons with higher levels of neuronal excitability would be more sensitive to stress both because their hyperexcitable neurons would abnormally amplify stress and because, over time, their hyperexcitable neurons would accelerate stress-induced kindling [19, 22]. Persons with higher levels of neuronal excitability would also be more likely to experience symptom-cycling because highly excitable neurons would have a greater propensity to facilitate aberrant circuit induction [23]. Treatment with antidepressants would further increase this risk because antidepressants (including SSRIs) have stimulatory effects on the brain [71, 72]. Hypothetically, this is what places such patients, who could be categorized as "bipolar spectrum," at elevated risk for bipolar switching when treated with antidepressants. The more appropriate drugs for such patients would be anticonvulsants. Yet, because the symptom-cycling in such patients is often subclinical [42-44], and because neuronal hyperexcitability also tends to cause symptoms of ADHD [22], the vast majority of such patients are treated with antidepressants and psychostimulants. What creates even more confusion is that these drugs do tend to reduce symptoms, at least until the kindling that they fuel increases the overall level of excitation in the brain enough to offset their therapeutic effects [72, 73]. Until now, the failure to recognize this and the continued treatment of symptoms rather than neuropathology in psychiatric patients has resulted in the over-prescribing of antidepressants, psychostimulants, and other psychotropic drugs in lieu of anticonvulsants [28]. That is not to say that antidepressants are never helpful but only to say that they are more appropriate for the minority of patients who do not have hyperexcitable neurons. Such patients, who could be categorized as "true" unipolar depressives because of their relative resistance to symptom-cycling would, for the same reason, be unlikely to cycle even when treated with stimulating antidepressants. This is the MCNH explanation for why treatment with antidepressants has generally been found to be safer in patients with unipolar depression [74] than bipolar spectrum disorder [32, 75, 76]. However, considering the rarity of true unipolar depression in comparison to the high frequency with which antidepressants are prescribed [22, 77], the MCNH hypothesis also points to the weakness of symptoms alone as a guide to psychiatric pharmacotherapy.

Clearly, the idea of treating nearly all of the common psychiatric disorders by reducing the excitability of the neurological system would simplify drug selection because it would highlight a biological target for which the treatment is evident. Thus, rather than chasing after specific symptoms with different classes of medication, such as anxiety symptoms with benzodiazepines, depressive symptoms with antidepressants, and psychotic symptoms with antipsychotics, a single non-benzodiazepine anticonvulsant or combination of anticonvulsants could be used to reduce all of these symptoms simultaneously. Note that in addition to simplifying drug selection and reducing medication load, this approach, which could be called "focused neuroregulation [78]," would circumvent the problem of ambiguous and overlapping diagnoses. Additionally, by reducing the total number of medications prescribed and replacing many brand-name drugs with generic ones, focused neuroregulation has the potential to reduce the side effect burden, medication costs, and conflicting effects that combining drugs from different classes can create. It also has the potential to simplify drug titration because anticonvulsants, which, based on their putative mechanism of action, could more aptly be called "neuroregulators" [79], exert their therapeutic effects in minutes rather than weeks. That means a patient could be started on a neuroregulator at an extremely low dosage and then titrated upward every one-to-two days rather than one-to-two weeks, as would be necessary with an antidepressant. It also means that any drug that was ineffective could be replaced much faster than when a drug takes several weeks to take effect. Moreover, because neuroregulators work to normalize brain function rather than modulate the activity of specific neuronal circuits, they can be combined with one another with relatively little risk of destabilizing mood, hence the term "mood stabilizer" [80-84].

V. Medication Dosing

The overprescribing of psychotropic drugs is not the only problem that begs to be addressed in modern clinical practice. The other is the dosing of psychotropic drugs. There are numerous factors that contribute to determining the optimal dosage of a medication for an individual patient. These include absorption and distribution, mechanism of action, receptor affinity, and metabolism and excretion. Although absorption and distribution are commonly assumed to be the most important of these, the actual contribution that each factor makes is highly specific to the individual. That underscores the importance of tailoring to the patient the quantity of drug prescribed.

a) Absorption and Distribution

Regardless of the quantity of a drug one ingests, the drug remains outside the body until it is absorbed through the intestinal wall. This absorption process can be affected by many factors, including drug solubility, intestinal membrane permeability, digestive enzyme activity, and food intake [85]. Drug absorption can also be affected by a person's emotional state, as stress tends to reduce intestinal absorption [86]. Furthermore, once in the bloodstream, the drug must cross the blood-brain barrier (BBB) before it can bind to its target receptors in the brain. Passage through the BBB can be affected by several factors, including the chemical properties of the drug, whether or not the drug is bound to plasma proteins, and the electrical charge of the drug [87]. While most small lipophilic drugs may cross the BBB by simple diffusion, others may pass through aqueous channels or require either mediated diffusion or active transport. Additionally, only free (non-protein-bound) molecules are available to cross the BBB via transendothelial diffusion, and fat-soluble drugs may be absorbed into fatty tissue, thus reducing their bioavailability. Together, all of these time-dependent factors contribute to the 20-40-minute delay in the onset of action of most medications. Obviously, the route of administration is also important, as absorption can be facilitated by direct inhalation of a drug, chewing and sublingual holding of a drug, or injection of a drug subcutaneously, intramuscularly, or intravenously. Thus, numerous factors can affect the speed and extent to which a drug actually reaches its target receptors.

b) Mechanism of Action

Because the number of different pathological processes that can occur in the human body far outnumber the assortment of ways that those processes can be expressed clinically, many different pathological processes can precipitate the same signs and symptoms. This highlights the importance of fit between drug selection and pathological process in determining the dosage requirements of a particular drug. The more that a drug's pharmacological effects can correct, offset, or compensate for the abnormality that is driving the patient's symptoms, the more efficiently the drug will work and, thus, the less of the drug that will be needed to express its therapeutic effects.

c) Receptor Affinity

In order for most drugs to exert their therapeutic effects, the molecules of the drug, like keys fitting into locks, must bind to and activate their target receptors. Although most receptors within a species are very similar in size and shape, there are also minor differences, just as there are in one's head-size, hand-size, and foot-size. This can affect the ability of specific drugs to bind to and activate their target receptors. The better the fit between the drug and the receptor, the more likely the drug is to exert its therapeutic effects. Also, the greater the drug's affinity for the receptor, the less of the drug that will be needed to maintain its therapeutic effect. However, a drug can also cause side effects if it binds to off-target receptors. This underscores the importance of finding the sweet spot when dosing psychotropic drugs.

d) Metabolism and Excretion

Immediately after a drug enters the bloodstream, the processes of distribution, metabolism, and excretion begin. Hence, dosing requirements can depend highly on fat solubility, liver enzyme activity, and glomerular filtration rates. Total blood volume and body weight also contribute to dosing requirements; however, these two factors generally pale in comparison to the many other factors that affect the dosing requirements of a drug.

VI. The Need for Individualized Dosing

With all of the aforementioned factors influencing the dosage of a drug that is needed to achieve a therapeutic effect and, conversely, unwanted side effects, there is clearly a need for individualized dosing of any drug that is prescribed. Yet most prescribers simply initiate treatment at the "recommended" starting dose or lowest available dosing strength. Clearly, however, this fails to align with the complexity and unpredictability of patient-specific factors. Then again, even if a prescriber were to take into consideration all of the aforementioned factors, there would still be no reliable way to determine how those factors come together to predict the therapeutic dose (and side effect dose) of a given drug for a given individual.

In recent years, however, various new pharmacogenomic tests have been developed to help clinicians determine which medications would be best tolerated by which patients. The problem is that these tests, though genetically-based, fail to incorporate the many other factors besides drug metabolism that influence the dosing requirements of a particular drug for a particular patient. Dosing requirements would also depend upon the degree of fit between the drug's primary mechanism of action and the type of pathology that is being treated. This has been particularly problematic in psychiatry due to the lack of clarity about what pathological process is being treated and the continued reliance on symptoms rather than pathology as a guide to pharmacotherapy. This reiterates the importance of replacing the current (symptom-based) approach to psychiatric diagnosis and treatment with a pathology-based approach.

VII. Toward Improving the Precision of Psychotropic Drug Dosing

With so many variables affecting dosing requirements, the safest and most accurate way to titrate psychotropic drugs, like most other drugs, is to start low and go slow. Another helpful practice is to consider a patient's ethnic background, as some ethnic groups, such as Asians, tend to be slow metabolizers of some drugs [88, 89]. Still, the problem with a gradual titration is that it can delay clinical improvement by weeks or even months because antidepressants, which in psychiatry are the most commonly prescribed drugs, take several weeks to exert their therapeutic effects. This is in-part what drove the development of the new pharmacogenomic tests. It was thought that by coordinating drug selection to a patient's enzyme activity, antidepressant therapy could be initiated at doses closer to the therapeutic dose without significantly increasing the risk of medication side effects. However, as previously discussed, the many other factors that influence dosing requirements besides metabolism can cause the genomic testing results to be misleading. Therefore, it is also important to review the patient's experience with other medications that may have been tried, particularly those in the same class as the proposed medications. This can be very helpful because an individual's sensitivity to medication tends to generalize across drug classes and across medications within a given class. Yet another dosage guide, and one that is seldom utilized, is the history of drug sensitivities in the patient's parents, siblings, and other blood relatives. If high drug sensitivity is found to run in a patient's family, the clinician should allow the patient to fractionate the lowest available dosage of any newly-prescribed medication. If the starting dose is found to be well-tolerated, the patient can simply take a little more of the medication. An added benefit of this conservative approach is that the unlikelihood of side effects gives the patient a little more time to overcome any apprehension about starting a new psychotropic drug. It is far better for a patient to become impatient with a new drug than to become frightened of it due to initial side effects. These simple precautionary measures can, in some cases, make the difference between a successful outcome with a drug and an outcome that leaves the patient unwilling to take any more of the drug or, worse yet, any other psychotropic drug.

Another cautionary note with regard to drug dosing is the use of serum levels. Although obtaining a blood level can be helpful in some cases, blood levels should not be used as a substitute for close clinical monitoring during dosage titration. That's because blood levels do not take into account the possibility that a particular patient may be highly responsive to a drug, thus allowing lower-than-average blood levels to achieve an adequate therapeutic effect. In many cases, these lower blood levels can prevent the occurrence of side effects without compromising effectiveness because most drugs exert their optimal therapeutic effects at a dosage just below their side effect dosage. Where blood levels are most useful is in the monitoring of patients who, for the various reasons described earlier, require unusually high doses of a particular medication in order to achieve a therapeutic effect. In such cases, obtaining a blood level can be used to justify the need for higher dosing and can also be used to substantiate any suspicions of medication non-compliance or drug diversion. Unfortunately, far too many patients are allowed to bear unnecessary side effects simply because the prescriber felt the need to maintain the serum level within the "therapeutic range."

VIII. Discussion

The goal of this article was to address the problems of diagnostic confusion, psychotropic drug overprescribing, and side-effect burden due to a lack of precision in the treatment of psychiatric disorders. All of these problems could potentially be minimized by applying an emerging hypothesis that contends that psychiatric symptoms are the consequence of cognitive-emotional stress superimposed upon a pathological hyperexcitability of the neurological system. Fortuitously, targeting this problem with neuroregulators yields rapid results, thus allowing the medications to be started at comfortably low doses and rapidly titrated to clinical improvement. In so-doing, the risk of side effects is minimized without substantially extending the time to therapeutic effect. Also, by remaining focused on the biological target, focused neuroregulation streamlines treatment, thus circumventing the need to use combinations of drugs that, being directed at symptoms rather than neuropathology, may have competing or even paradoxical effects. Anecdotally, focused neuroregulation has yielded far more improvement, in far less time, and with far less side effects than standard antidepressant therapy in a wide range of psychiatric disorders, including the majority of patients who would, based on current nosology, be diagnosed with major depressive disorder or dysthymia. Moreover, in nearly all of these patients, some of whom have been observed for more than two decades, the initial benefits have been maintained without any need of further dosage adjustment.

Although anticonvulsant neuroregulators are also used to treat epilepsy, the dosage of these drugs can usually be lower when treating psychiatric disorders because the target abnormality, namely neuronal hyperexcitability, is entirely reversible. This is in contrast to seizure disorders, in which the excitability of the neurological system might need to be brought to subnormal levels in order to compensate for the structural abnormality that may be lowering the seizure

threshold. Thus, for example, while the average dosage of oxcarbazepine needed to prevent seizures typically ranges between 600mg and 1200mg per day, the average dosage needed to prevent psychiatric symptoms typically ranges between 150mg and 600mg per day. In fact, some psychiatric patients have been observed to respond to oxcarbazepine doses as low as 50-100mg per day. The same phenomenology has been observed with other anticonvulsants, such as gabapentin, depakote, lamotrigine, and topiramate [90]. Of course, lower dosing is also easier when treating psychiatric disorders because, unlike when treating seizure disorders, the therapeutic effect is observable almost immediately. What's more, anticonvulsant stacking, which is commonly employed in neurology, is not only effective in psychiatry but is apt to be even more effective than in neurology because the target abnormality is entirely reversible. Indeed, it has been said that the potential benefits of anticonvulsants in the treatment of psychiatric disorders may overshadow those that have been observed in the treatment of seizure disorders [91]. Long-term, anticonvulsants may even be protective against the development of various disease states [67, 68].

IX. Directions for Future Research

Urgently needed are clinical studies comparing the benefits of focused neuroregulation to standard treatment for a variety of psychiatric disorders. Such studies should also compare the number of different medications needed to control symptoms, the side effect burden of those medications, and the duration of effect of those medications. They should also compare the effect of those medications on resting heart and respiratory rate measurements. If these studies yield promising results, longer-term prospective studies could be performed to assess the potential for early treatment with neuroregulators to delay or even prevent the development of various chronic diseases.

X. Conclusion

The well-recognized problems of diagnostic ambiguity, polypharmacy, and side-effect burden in the treatment of psychiatric disorders has the potential to be solved by shifting the treatment of these disorders from a symptom-based approach to a pathology-based approach. Guided by the MCNH hypothesis, neuroregulators could be started at comfortably low doses and then titrated rapidly to clinical improvement. Because neuroregulators work to normalize brain function, they can also be combined with one another just as they are in the treatment of epilepsy. Moreover, because neuronal hyperexcitability tends to dysregulate virtually every system of the body, treatment with neuroregulators could be as medically protective as it is psychiatrically beneficial. With less than half of all persons who need psychiatric care actually seeking care, and many of those who do seek care shying away from psychotropic medication, the need for better education about what abnormality is being treated and a more targeted approach that uses fewer medications, at lower doses, and with fewer side effects is evident. All of these needs could potentially be met by targeting what is hypothesized to be the underlying driver of mental illness. By seizing this long-awaited opportunity, we can strive toward a future in which behavioral healthcare, like other fields of medicine, is aimed at specific pathological processes, thus streamlining care, speeding recovery, and helping to overcome the long-held stigma of mental illness.

Conflicts of Interest

The author declares that he has no competing interests.

References Références Referencias

1. Voineskos D, Daskalakas, ZJ, Blumberger, DM. Management of treatment-resistant depression: challenges and strategies. Neuropsychiatric Disease and Treatment 2020; 16: 221-234.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D Report. American J. Psychiatry 2006; 163 (11): 1905-1917.
3. Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy inpsychiatry: A review. Mens Sana Monogr 2013; 11 (1): 82-99.
4. Mental health has bigger challenges than stigma. Rapid Report Mental Health Million Project 2021. https://mentalstateoftheworld.report/wp-content/uploads/2021/05/Rapid-Report-2021-Help-Seeking.pdf. (Accessed 7/20/2023).
5. Conroy J, Lin L, Ghaness A. Why people aren't getting the care they need. American Psychological Association 2020; 51 (5).
6. The Brainstorm Consortium. Analysis of shared heritability in common disorders of the brain. Science 2018; 360 (6395): eaap 8757.
7. Akiskal HS. The bipolar spectrum: new concepts in classification and diagnosis. In: Grinspoon L, editor. Psychiatry Update; The American Psychiatric Association Annual Review. Vol. 2. Washington DC: American Psychiatric Press1983, pp. 271–292.
8. Koukopoulos A, Tundo A. A mixed depressive syndrome. Clin Neuropharmacol1992; 15 (Suppl 1) (Pt A): 626A–627A.
9. Koukopulos A, Reginaldi P, Laddomada G, et al. Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol1980; 13: 156–167.
10. Patten SB, Paris J. The bipolar spectrum—A bridgetoo far?La Revue canadienne de psychiatrie 2008; 53 (11).

11. Delgado PL. Depression: the case for a monoamine deficiency. J Clin Psychiatry. 2000; 61 Suppl 6: 7-11.
12. Hirschfeld R. History and evolution of the monoamine hypothesis of depression. Journal of Clinical Psychiatry 2000; 61 (6): 4-6.
13. Neumeister A, Nugent AC, Waldeck T, et al. Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. Arch Gen Psychiatry 2004; 61: 765-773.
14. El-Mallakh RS, Vöhringer PA, Ostacher MM, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. Journal of Affective Disorders 2015; 184: 318-321.
15. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disorders 2001; 5 (6).
16. Truman CJ, Goldberg JF, Ghaemi SN. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 2007; 68 (10): 1472-1479.
17. Henry C, Sorbara F, Lacoste J, Gindre C, Leboyer M. Antidepressant-induced mania in bipolar patients: Identification of risk factors. J Clin Psychiatry 2001; 62 (4): 249-255.
18. Yamaguchi Y, Kimoto S, Nagahama T, Kishimoto T. Dosage-related nature of escitalopram treatment-emergent mania/hypomania: a case series. Neuropsychiatr Dis Treat 2018; 14: 2099-2104.
19. Binder MR. Mind-brain dynamics in the pathophysiology of psychiatric disorders. Am J Psychiatry and Neurosci 2022; 10 (2): 48-62.
20. Binder MR. The multi-circuit neuronal hyperexcitability hypothesis of psychiatric disorders. AJCEM 2019; 7 (1): 12-30.
21. Binder MR. Probing the link between substance use and psychiatric disorders: Toward a new paradigm in the treatment and prevention of these intertwined disorders. Int J Psychiatry Res 2023; 6 (3): 1-13.
22. Binder MR. The neuronal excitability spectrum: A new paradigm in the diagnosis, treatment, and prevention of mental illness and its relation to chronic disease. AJCEM 2022; 10 (1): 1-7.
23. Binder MR. Electrophysiology of seizure disorders may hold key to the pathophysiology of psychiatric disorders. AJCEM 2019; 7 (5): 103-110.
24. Binder MR. Neuronal hyperexcitability: Significance, cause, and diversity of clinical expression. AJCEM 2021; 9 (5); 157-167.
25. Binder MR. FLASH syndrome: Tapping into the root of chronic illness. AJCEM 2020; 8 (6): 101-109.
26. Binder MR. Suicide: A new hypothesis on the pathogenesis of disease, method of screening, and means of prevention. AJPN 2022; 10 (3): 111-124.
27. Binder MR. Neuronal hyperexcitability: The elusive link between social dysfunction and biological dysfunction. World J Public Health 2022; 7 (3): 99-110.
28. Binder MR. Anticonvulsants: The psychotropic and medically protective drugs of the future. AJCEM 2021; 9 (5): 174-182.
29. Binder MR. Illicit use of gabapentin may reveal more about the drug's benefits than its liabilities. American J Int Med 2022; 10 (6): 114-121.
30. Post RM, Denicoff KD, Frye MA, et al. A history of the use of anticonvulsants as mood stabilizers in the last two decades of the 20th century. Neuropsychobiology 1998; 38 (3): 152-166.
31. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016; 30 (6): 495-553.
32. Shah B, Elsayed OH, El-Mallakh RS. Bipolar disorder: The foundational role of mood stabilizers. Current Psychiatry 2023; 22 (5): 36-41.
33. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63 (8): 856-864.
34. Newport DJ, Carpenter LL, McDonald WM, et al. APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015; 172 (10): 950-966.
35. Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. N Engl J Med2019; 381 (10): 903-911.
36. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: A randomized clinical trial. JAMA Psychiatry 2021; 78 (9): 951-959.
37. Zorumski CF, Paul SM, Covey DF, Mennerick S. Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond. Neurobiology of Stress 2019; 11: 100196.
38. Kreston R. (2016) The psychic energizer! the serendipitous discovery of the first antidepressant - Body Horrors. http://blogs.discovermagazine.com/bodyhorrors/2016/01/27/2 081/. (Accessed 10/2/18).
39. Cuellar AK, Johnson SL, Winters R. Distinctions between bipolar and unipolar depression. Clin Psychol Rev 2005; 25 (3): 307-339.
40. Ghaemi SN. Bipolar spectrum: a review of the concept and a vision for the future. Psychiatry Investig 2013; 10 (3): 218-224.

41. Miller CJ, Johnson SL, Eisner L. Assessment tools for adultbipolar disorder. Clin Psychol (New York) 2009; 16 (2): 188-201.
42. Hirschfeld R, Lewis L, Vornik L. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003; 64 (2): 161-174.
43. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. The Canadian Journal of Psychiatry2016; 64 (4).
44. Campbell D. People with bipolar disorder may wait 13 years for diagnosis. The Guardian. https://www.theguardian.com/society/2012/jun/27/bipolar-disorder-diagnosis-survey. (Accessed 10/7/18).
45. Binder MR. Am I depressed or am I bipolar? Lightning source Publishers 2009.
46. Binder MR. [Chicago Mental Health]. The racing mind video series, part 5: Bipolar disorders & neuronal hyperexcitability. [Video] YouTube 2021. https://youtu.be/GJC4oYKcT1c.
47. Latvala A, Kuja-Halkola R, Rick C, et al. Association of resting heart rate and blood pressure in late adolescence with subsequent mental disorders: A longitudinal population study of more than 1 million men in Sweden. JAMA Psychiatry 2016; 73 (12): 1268-1275.
48. Blom EH, Serlachius E, Chesney MA, Olsson EMG. Adolescent girls with emotional disorders have a lower end-tidal CO2 and increased respiratory rate compared with healthy controls. Psychophysiology 2014; 51 (5): 412-418.
49. Colangelo LA, Yano Y, Jacobs Jr DR, Lloyd-Jones DM. Association of resting heart rate with blood pressure and incident hypertension over 30 years in black and white adults: The CARDIA study. Hypertension 2020; 76 (3): 692-698.
50. Shi Y, Zhou W, Liu S, et al. Resting heart rate and the risk of hypertension and heart failure: a dose-response meta-analysis of prospective studies. J Hypertens 2018; 36 (5): 995-1004.
51. Shen L, Wang Y, Jiang X, et al. Dose-response association of resting heart rate and hypertension in adults: A systematic review and meta-analysis of cohort studies. Medicine (Baltimore) 2020; 99 (10): e19401.
52. Dalal J, Dasbiswas A, Sathyamurthy I, et al. Heart rate in hypertension: Review and expert opinion. International Journal of Hypertension 2019; 2019.
53. Lee DH, de Rezende LFM, Hu FB, Jeon JY, Giovannucci EL. Resting heart rate and risk of type 2 diabetes: a prospective cohort study and meta-analysis. Diabetes Metab Res Rev 2019; 35 (2): e3095.
54. Aune D, o'Hartaigh B, Vatten LJ. Resting heart rate and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of cohort studies. Nutr Metab Cardiovasc Dis 2015; 25 (6): 526-534.
55. Nagaya T, Yoshida H, Takahashi H, Kawai M. Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type-2 diabetes mellitus. Int J Epidemiol 2010; 39 (1): 215-222.
56. Kannel W, Kannel C, Paffenbarger R, Cupples A. Heart rate and cardiovascular mortality: The Framingham study. Am Heart J 1987; 113: 1489-1494.
57. Gillum R, Makuc D, Feldman J. Pulse rate, coronary heart disease, and death: The NHANES I epidemiologic follow-up study. Am Heart J 1991; 121: 172-177.
58. Cooney MT, Vartiainen E, Laatikainen T, et al. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010; 159 (4): 612-619.
59. Khan H, Kunutsor S, Kalogeropoulos AP, et al. Resting heart rate and risk of incident heart failure: three prospective cohort studies and a systematic meta-analysis. J Am Heart Assoc 2015; 4 (1): e001364.
60. Alhalabi L, Singleton MJ, Oseni AO, et al. Relation of higher resting heart rate to risk of cardiovascular versus noncardiovascular death. Am J Cardiol 2017; 119 (7): 1003- 1007.
61. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ 2016; 188 (3): E53-E63.
62. Aune D, Sen A,o'Hartaigh B, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis 2017; 27 (6): 504-517.
63. Anker MS, Ebner N, Hildenbrandt B, et al. Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. European Journal of Heart Failure 2016; 18 (12).
64. Park J, Kim JH, Park Y. Resting heart rate is an independent predictor of advanced colorectal adenoma recurrence. PLoS One 2018; 13 (3): e0193753.
65. Burke SL. Resting heart rate moderates the relationship between neuropsychiatric symptoms, MCI, and Alzheimer's disease. Innov Aging 2019; 3 (suppl 1): S641.
66. Jouven X, Empana J-P, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005; 352: 1951-1958.

67. Binder MR. Psychiatric and functional physical symptoms: The more telling "fifth" vital sign. AJCEM 2021; 9 (6): 233-337.
68. Binder MR. Neuronal hyperexcitability: The elusive but modifiable instigator of disease. AJCEM 2022; 10 (1): 1-7.
69. Gabapentin—The popular but controversial anticonvulsant drug may be zeroing in on the pathophysiology of disease. AJCEM 2021; 9 (4): 122-134.
70. Rose GM, Diamond DM, Pang K, Dunwiddie TV. Primed burst potentiation: lasting synaptic plasticity invoked by physiologically patterned stimulation. In: Haas HL, Buzsàki G. (eds) Synaptic plasticity in the hippocampus. Springer, Berlin, Heidelberg, 1988.
71. Khushboo SB. Antidepressants: mechanism of action, toxicity and possible amelioration. J Appl Biotechnol Bioeng 2017; 3 (5): 437-448.
72. Khedr EM, Elserogy Y, Fawzy M. Effects of psychotropic drugs on cortical excitability of patients with major depressive disorders: A transcranial magnetic stimulation study. Psychiatry Research 2020; 291: 113287.
73. Cooper DC, Moore SJ, Staff NP, Spruston N. Psychostimulant-induced plasticity of intrinsic neuronal excitability in ventral subiculum. J Neurosci 2003; 23 (30): 9937-9946.
74. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol2015; 29 (5): 459-525.
75. Frances AJ, Kahn DA, Carpenter D, Docherty JP, Donovan SL. The Expert Consensus Guidelines for treating depression in bipolar disorder. J Clin Psychiatry 1998; 59 Suppl 4:73-79.
76. Kahn DA, Sachs GS, Printz DJ, Carpenter D. Medication treatment of bipolar disorder 2000: A summary of the expert consensus guidelines. Journal of Psychiatric Practice 2000; 6 (4): 197-211.
77. Binder MR.A pathophysiolgically-based approach to the treatment and prevention of mental illness and its related disorders. AJCEM 2021; 9 (6): 223-232.
78. Binder MR. Focused neuroregulation in the treatment and prevention of mental and physical illness. AJCEM 2022; 10 (2): 49-58.
79. Binder MR. Introducing the term "neuroregulator" in Psychiatry. AJCEM 2019; 7 (3): 66-70.
80. Fergusson D, Doucette S, Glass KC,et al. Association between suicide attempts and selective serotonin reuptake inhibitors: Systematic review of randomised controlled trials. BMJ 2005; 330: 396-402.
81. Braun C, Bschor T, Franklin J, Baethge C. Suicides and suicide attempts during long-term treatment with antidepressants: A meta-analysis of 29 placebo-controlled studies including 6,934 patients with major depressive disorder. Psychother Psychosom 2016; 85 (3): 171-179.
82. Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. Am J Psychiatry 2006; 163 (5): 813-821.
83. Healy D. Let the eat prozac: The unhealthy relationship between the pharmaceutical industry and depression. New York: University Press; 2004.
84. Britton JW, Shih JJ. Antiepileptic drugs and suicidality. Drug, Healthcare and Patient Safety 2010; 2: 181-189.
85. Azman M, Sabri AH, Anjani QK, Mustaffa MF, Hamid KA. Intestinal absorption study: Challenges and absorption enhancement strategies in improving oral drug delivery. Pharmaceuticals (Basel) 2022; 15; (8): 975.
86. Lopresti AL. The Effects of psychological and environmental stress on micronutrient concentrations in the body: A review of the evidence. Adv Nutr 2020; 11 (1): 103-112.
87. Banks W. From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. Nat Rev Drug Discov 2016; 15 (4):275–92.
88. Lo C, Nguyen S, Yang C, et al. Pharmacogenomics in Asian subpopulations and impacts on commonly prescribed medications. Clin Transl Sci 2020; 13 (5): 861-870.
89. Olafuyi O, Parekh N, Wright J, Koenig J. Inter-ethnic differences in pharmacokinetics—is there more that unites than divides? Pharmacol Res Perspect 2021; 9(6): e00890.
90. Binder MR. Symptom instability as a predictor of response to mood stabilizers: A retrospective chart review of 300 consecutive inpatients and outpatients with symptoms of depression. 2005 (unpublished study).
91. Grunze HCR. The effectiveness of anticonvulsants in psychiatric disorders. Dialogues Clin Neurosci2008; 10: 77-89.

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The Link between Social Anxiety and Peripheral Inflammatory Markers in Patients with Schizophrenia Diagnoses

By Amelia Dias Teixeira, Victor Hugo Schaly Cordova & Paulo Belmonte-de-Abreu

Universidade Federal do Rio Grande do Sul (UFRGS)

Abstract- *Background:* It exist increasing studies on the inflammatory process in psychiatric disorders, in which inflammation in schizophrenia (SZ) isquestioned.

Objective: assess the association between social anxiety (SA) and inflammation in patients with SZ, measuring primarily the neutrophil-to-lymphocyte ratio (NLR) and secondarily the systemic immune-inflammation index (SII), monocyte-to-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR).

Methods: A cross-sectional study.

Results: Of the 82 patients who met the inclusion criteria, 59 patients had SA and observed a significant alteration in inflammation markers in patients with SZ, especially NLR.

Keywords: *social anxiety, schizophrenia, peripheral markers of inflammation, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index.*

GJMR-A Classification: *LCC: RC516*

Strictly as per the compliance and regulations of:

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Methods: A cross-sectional study.

Results: Of the 82 patients who met the inclusion criteria, 59 patients had SA and observed a significant alteration in inflammation markers in patients with SZ, especially NLR.

Conclusion: NLR was significantly higher when compared to the cut-off point in the general sample. The greater the severity of SZ symptoms, the higher the SA in these patients and patients with SA showed higher scores on Brief Psychiatric Rating Scale(BPRS)and Generalized Anxiety Disorder Scale(GAD-7), and the higher the SA scores, the higher the NLR, SII, and PLR. Our findings indicate that inflammation appears to be a characteristic of patients diagnosed with SZ, agreeing with the conclusions of the literature and that SA may cause an additional increase in inflammatory indices in these patients. In addition, inflammation was seen to interfere with SA, independent of the other variables.

Keywords: social anxiety, schizophrenia, peripheral markers of inflammation, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index.

I. Introduction

Schizophrenia (SZ) is a serious and complex mental disorder that affects around 1% of the world's population, causing damage to the patient and family, of multifactorial origin [1].Its diagnosis involves a set of signs and symptoms and impaired professional or social functioning [2]. Its symptoms affect perception, thought, affect, and behavior [3] without any pathognomonic symptoms [2] and involve distortions of perception about oneself and with external reality [1]. Two or more of the following symptoms are required for diagnosis: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms such as diminished emotional expression or avolition, with at least one of the symptoms being the first three [3]. Social anxiety (SA) or social phobia is not included among the necessary symptoms, but is frequent before the onset of the disorder [1] and can represent both a residual and a complication of the illness, contributing to great personal suffering and functional impairment after the acute phase of SZ.

SA can be defined by intense or heightened fear or anxiety of one or more social events in which the person is exposed to the likely evaluation of other individuals [2], as a result of negative assessment [2,4], the possibility of judgment or rejection [4]. It is an interpersonal, intrapersonal, and social system disorder, with impaired reciprocal interaction and communication, such as failure of social cohesion and rejection, emotional and physical feelings such as nervousness and sweating, avoidance attitude of feared situations, and dysfunctional beliefs in social situations or imagining these events [5]. Fear, anxiety or avoidance in people with SA, or social phobia imply clinically significant distress or impairment in social, occupational, or other essential spheres of functioning [2].

Several peripheral markers derived from blood count have been increasingly used as an indirect measure of inflammatory activity in the brain in psychiatric disorders [6-10], calculated under simple laboratory exams [10], from a complete blood count [6,11-13].

The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR)and platelet-to-lymphocyte ratio (PLR) have been investigated as clinical circulating markers of chronic inflammation in many diseases [9,10,14-17], especially NLR [7,8,18]which constitutes baselines of the innate (neutrophil) and adaptive (lymphocyte) immune systems [6,19,20]and may be less affected by confounding variables, being an effective biomarker to identify patients who may benefit from pharmacological

Author α σ ρ: Graduate Program in Psychiatry and Behavioral Sciences, Schoolof Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.
Author ρ: Department of Psychiatry and Forensic Medicine, Schoolof Medicine. Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.
Corresponding Author α: Amelia Dias Teixeira, Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Campus Saúde. Rua Ramiro Barcelos, 2400, 2º andar. 90035003 - Porto Alegre, RS – Brasil.
e-mail: amelia_psico@hotmail.com

treatment adjuvant anti-inflammatory [6] and therefore more reliable in severe mental disorders [10,19].

Many authors cite the hypothesis of frequent inflammation in SZ [6,7,9,10,17,18], both in pathogenesis [7,9] and pathophysiology [18], where the lymphocyte count was lower and that of neutrophils considered higher in schizophrenics patients [7,9,17].

Moreover, a new index, defined as the systemic immune-inflammation index (SII), based on the count of lymphocytes, neutrophils and platelets [13,16,21,22], has been considered a good index [22], and even a better index to reflect local immune response and systemic inflammation, as its high predictive value has been confirmed in a variety of tumors [13,22], brain infarction, cardiovascular disease, and acute pancreatitis [13].

In addition, there may be a connection between anxiety disorders and inflammation, in which the immune system and inflammation play a role. It is suggested the values of NLR [6,23], MLR and PLR are significantly higher in this disorder, even with a limited number of studies [22]. Despite these two independent observations of increased inflammatory markers in SZ and SA, there are no studies, as long we identified, addressing comorbid SZ-SA and checking if the simultaneous SZ-SA diagnosis may reveal increased inflammation.

II. Objective

Assess the association between social anxiety (SA) and inflammation in patients diagnosed with schizophrenia (SZ), measuring primarily the NLR, and secondarily the SII, MLR and PLR.

III. Methods

It´s about a cross-sectional study of the association between comorbid AS in SZ and levels of peripheral markers of inflammation, especially NLR.

The first hypothesis is the increased inflammation (revealed by increased NLR) in patients with comorbid SZ-SA compared to patients with SZ without SA. The second hypothesis is that the other markers (SII, MLR and PLR) are also altered in schizophrenics patients with SA than without SA.

The sample comprised 82 patients attending the schizophrenia outpatient clinic of a major teaching hospital in southern Brazil (Hospital de Clínicas de Porto Alegre- HCPA) under the Public Health System, diagnosed with schizophrenia of both genders and aged between 18-70 years. Patients with other psychiatric diagnoses, active or chronic inflammatory or autoimmune diseases, and under treatment with anti-inflammatory or immunosuppressive medication were excluded.

All participants were aware of the research objectives and received an invitation to participate. Those who agreed to contribute to the study signed the Informed Consent Form (ICF) approved by the Ethics Committee of the HCPA. Patient´s medical records were also accessed and consulted to ascertain the information needed for the study.

a) Instruments

Liebowitz Social Anxiety Scale (LSAS): developed in 1987 by Michel Liebowitz and translated, adapted and validated in four languages [23]. It is a 24-item questionnaire that assesses fear/anxiety and avoidance in specific social situations [24] with 11 items related to social interaction and 13 items related to public performance [25]. Four-point scale ranging from 0 = none to 3 = severe, and the total score is obtained by adding the fear and avoidance columns [24,26]. As for the classifications of the scores, there is no consensus in the literature. We based ourselves on the Brazilian study by Dos Santos et al. [23]mentions 32 as a good value for the cut-off point, so we followed the following classification: mild social phobia (32-43 points), moderate (44-81) and severe (from 82 points).

Brief Psychiatric Rating Scale (BPRS): developed by Overall and Gorham, is one of the most widely used scales in psychiatric research; where it originally consisted of 16 items, but in 1966 had two additional things (arousal and disorientation), the BPRS-18 [27]. It is a 7-point Likert scale score, where 0 = absent, 1 = normal, 2 = borderline illness, 3 = mild illness, 4 = moderately ill, 5 = markedly ill, 6 = severely ill and 7 = extremely ill. The cut-off score for the remission of schizophrenia on the BPRS-6 was less than 5, while the ranges for mild, moderate, and severe severity were 5-9, 10-19, and greater than 20, respectively [28]. Some studies address the domains/dimensions of this scale [29-31], we based ourselves on that of Van Dorn et al. [31]for the following classification: positive domain (items ideas of grandeur, distrust, hallucinatory behavior, and altered thought content), negative (affective withdrawal, psychomotor retardation, and blunted affect), affective (somatic worry, anxiety, feelings of guilt, depressed mood, and hostility), and cognitive disorganization (conceptual disorganization, tension, mannerisms and posture, lack of cooperation, excitement, and disorientation).

Generalized Anxiety Disorder Scale (GAD-7): is a 4-point Likert scale (0-3) ranging from "never" to "every "day", asking how often the patient was bothered. The index is obtained by summing the scores, with cut-off points 5, 10, and 15 allowing the classification of anxiety into none/normal (0-4), mild (5-9), moderate (10-14), and severe (15-21) [32].

Blood count: through a blood test of the patient, to measure biomarkers of inflammation. The complete blood count is routinely collected at the outpatient clinic and included in patients' charts. Some patients have

their CBC performed elsewhere, and the patient or family member is asked to access it (we had eight cases in these conditions).

b) Statistical Analysis

Data analysis was performed using the Statistical Package of Social Science (SSP) software version 27.0, where 82 individuals were analyzed. A descriptive analysis was made of the clinical and sociodemographic characteristics of the total sample and both groups, shown as mean and standard deviation or frequency and percentage. Quantitative variables (inflammation markers, age, time of diagnosis of schizophrenia, number of psychiatric hospitalizations) were described using the mean and standard deviation or median and interquartile range. Categorical variables (gender, family income, education, scales, medications, comorbidities) were described by absolute frequencies and percentages.

The t-student test was used to compare means between the groups with social anxiety and without social anxiety. In the case of asymmetry, the Mann-Whitney test was applied. Pearson's chi-square or Fisher's exact tests were used to compare proportions. Spearman's correlation coefficient was applied to evaluate the correlations between the inflammation markers and the scales under study. Wilcoxon's test was used to compare Liebowitz Scale items about fear and avoidance and between performance and social anxieties. The significance level adopted was 5% ($p<0.05$).

To control for possible confounding variables, multivariate Poisson Regression analysis was used to assess factors independently associated with social anxiety. The criterion for entering the variable in the model was that it had a p-value <0.20 in the bivariate analysis. The standard for remaining in the final model was that it had a p-value <0.10. The effect measure used was the Prevalence Ratio (PR) and the 95% confidence interval.

c) NLR, SII, PLR, and MLR values

There are several studies of typical values for NLR, such as that of Forget [15], in the Belgian adult, non-geriatric population with good health status (between 0.78 and 3.53); Iranian population (NLR 1.70±0.70, MLR 11.15±3.14 and PLR 117.05±47.73, respectively[12]); Chinese (NLR 18-65 years old female =0.85-3.06 and male = 0.90-2.94, PLR 61-179, MLR female (0.10-0.32) and male (0.12-0.35) and IIS (161-761)[16]; IIS had a cut-off value of 679.96 (Adali etal. [36]) in research in Turkey.

Cut-off points for patients with squamous cell carcinoma of the external auditory canal with and without preoperative recurrence and those considered ideal were 3.75 × 109/L for neutrophil count, 1.77 × 109/L for lymphocyte count, 2.325 for NLR, 157.9 for PLR, and 3.065 for LMR[34]. Szor[35] studied the Brazilian population, with the cut-off value for NLR was 2.44; Eyff et al.[36] also studied Brazilian adults, with cut-off points for NLR and PLR of 2.80 and 362, respectively.

For the present study, we used the following cut-off points: 2.80 for NLR, 761 for SII, 0.35 for MLR, and 362 for PLR.

IV. Results

a) Sample Specifics

As shown in the flowchart in Figure 1, 140 patients were screened and 45 patients were excluded, 15 of these because the electronic medical records did not show a diagnosis of schizophrenia, 06 because they were in the telemedicine care modality, and 24 because they did not accept to participate in the research.

We interviewed 95 patients and excluded 13 patients, 10 of them because they presented other diagnoses (schizoaffective disorder, bipolar disorder, autism, acute psychotic disorder, psychosis due to cognitive disease, organic personality disorder) and 03 patients because of missing information and did not answer all the scales.

As a result, the sample ended up comprising 82 patients, 61 of whom (74.4%) were men and 21 (25.6%) women. The mean age was 47.3 years, and the most frequent schooling was complete high school (47.6%), followed by entire elementary school (32.9%).

As for the clinical characteristics, the mean ages of onset and duration of schizophrenia were 21.9 years and 25.4 years, respectively. The median number of psychiatric hospitalizations was two. The frequency of patients with comorbidities was 79.3%, and the main comorbidities found in these patients were obesity (28%), dyslipidemia (17.1%), smoking (15.9%), and diabetes (14.6%). Most patients were being treated with Clozapine (96.3%) and 31.7% were using other antipsychotics. The other most used drugs were Clonazepam (37.8%) and Amitriptyline (12.2%).

There were no significant differences in all variables between the groups with SA and without SA ($p>0.050$).

b) Social anxiety in schizophrenia

In the present investigation, of the 82 patients meeting the inclusion criteria, 59 patients (72%) had AS comorbidity, with scores higher from 32 in the LSAS, 12.2% being at a mild level of AS, 29.3% moderate, and 30.5% severe.

To complement the study, generalized anxiety was calculated in these patients using the GAD-7 scale, in which 32.9% of patients were at a mild level, 26.8% moderate and 7.3% severe. On the BPRS scale, the classification of the groups was 8.5%, 31.7% and 54.9% in mild, moderate and severe scores, respectively.

c) Social anxiety and inflammation in schizophrenia

The descriptive statistical analysis with the prevalence of the scores of the scales and markers of inflammation (CBC) in the total sample can be seen in Table 1. There was a significant difference in NLR, with 42.7% above the estimated cut-off point. There were also changes in the MLR (30.5%) and SII (25.6%), with no changes in the PLR (0.0%). It is also noted that in addition to 72% of patients showing SAD, 67.1% also had generalized anxiety.

The correlations between the LSAS, GAD-7, and BPRS scales with the inflammation markers NLR, SII, MLR, and PLR are shown in Table 2. There was a statistically significant positive correlation between the LSAS and the NLR, SII, and PLR markers, and the higher the SA scores, the higher the values of these markers; there was no correlation with MLR ($p>0.50$), as can also be seen in Figures 2 to 4. No correlation was also obtained between the GAD-7 and BPRS scales with inflammation markers.

It was It was observed an association of increased GAD-7 and BPRS with increased NLR only in patients with comorbid SA (LSAS score ≥ 32 points) (Table 3), and a trend of MLR and IIS failing to reach statistical significance. There were no PLR altered levels.

After adjustment by the multivariate model (table 4), the following variables remained significantly and independently associated with SA: GAD7 ≥ 5 points ($p=0.029$), positive, cognitive disorganization, and total domains of the BPRS ($p=0.003$, $p=0.004$ and $p=0.001$, respectively) and NLR ≥ 2.80 ($p<0.001$).

Patients who score five points or more on the GAD-7 scale, i.e. who show generalized anxiety at some level, have a 53% higher prevalence of AS compared to those who score less than five points (no generalized anxiety), regardless of BPRS and NLR.

Patients with one point more in the Positive and Cognitive Disorganization domains of the BPRS have a 4%growth in the prevalence of SA. As for the total score of this same scale, the increase is 2%, regardless of GAD-7 and NLR scores.

Finally, patients with an NLR equal to or greater than 2.80, which is the cut-off point, show a 55% increase in the prevalence of AS when compared to those with scores below 2.80 (no change in NLR), regardless of the GAD-7 and BPRS scales.

V. Conclusion

Social anxiety in schizophrenia arises from the difficulty of understanding social situations, where the person does not distinguish the intentions of others. Although it is not primary but secondary to the disease, it promotes excellent harm and disability in these patients, even with stabilized psychosis.

As shown above, we found the prevalence of 72% of SA in patients diagnosed with schizophrenia attending HCPA outpatient clinic. NLR was significantly higher in patients with comorbid SA compared to schizophrenic patients without this condition.

It was observed the severity of schizophrenia symptoms was associated with increased frequency of SA, with patients with SA with increased BPRS and GAD-7 scores. There also appeared to be a greater degree of inflammation in schizophrenia patients with SA, specially NLR, with increased SA scores associated with increased NLR, SII, and PLR (and no association with MLR).

Our findings support previous studies of increased inflammation in schizophrenia and provide new evidence that comorbid SA in people with schizophrenia is linked to increased inflammatory indices. However the design cannot tell us about causality.

In addition to the link between markers of inflammation and social anxiety in patients with schizophrenia, we saw that NLR interferes with SA and this is independent of schizophrenia.

Finally, since the analyzed factors were independence, we concluded that SA depends on the degree of schizophrenia and generalized anxiety, and inflammation caused by increased NLR and that these factors predict SA.

These findings become critical in thinking about new forms of treatment, addressing disability and impairment by social anxiety, with complementary therapies addressing inflammation that may modify the course and prognosis of the disease.

The results of these analyses may be limited by the modest sample size, but even so the results seem to have been significant. Not to mention the patients were interviewed by trained professionals and are being monitored by a team of residents and professors at the outpatient clinic where they have already been diagnosed.

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Disclosure

The authors report no conflicts of interest.

References Références Referencias

1. Silva AM, Dos Santos CA, Miron FM, Miguel NP, Furtado CC, Bellemo AIS. Schizophrenia: a literature review. UNILUS Journal Teaching and Research, 2016;13,30. ISSN 2318-2083.
2. American Psychiatric Association. DSM-5-TR: Diagnostic and statistical manual of mental disorders. Porto Alegre: Artmed; 2022.
3. Ruiz-Iriondo M, Salaberría K, Echeburúa E, Iruín Á, Gabaldón O, Fernández-Marañón I. Global

functioning among middle-aged patients with chronic schizophrenia: the role of medication, working memory and verbal comprehension. Anal. Psicol, Murcia, 2019; 35, 2, 204-213. ISSN 1695-2294. Doi: https://dx.doi.org/10.6018/analesps.35.2.336251.
4. Barzeva SA, Richards JS, Meeus WHJ, Oldehinkel AJ. The social withdrawal and social anxiety feedback loop and the role of peer victimization and acceptance in the pathways. DevPsychopathol. 2020; 32(4): 1402-1417. PMID: 31668152.
5. Hunger C, Hilzinger R, Klewinghaus L, Deusser L, Sander A, Mander J, Bents H, et. al. Comparing cognitive behavioral therapy and systemic therapy for social anxiety disorder: randomized controlled pilot trial (sopho-cbt/st). Family Process, 2020; 59(4): 1389-1406. Doi: doi: 10.1111/famp.12492. Epub 2019 Oct 27.
6. Brinn A, Stone J. Neutrophiltolymphocyte ratio in psychiatric diagnoses: a cross-sectional study using electronic health records. BMJ Open, 2020; 10: e036859. Doi: http://dx.doi.org/10.1136/bmjopen-2020-036859
7. Kulaksizoglu B, Kulaksizoglu S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. Neuropsychiatric Disease and Treatment. 2016: 12,1999–2005. PMCID: PMC4991539. Doi: 10.2147/NDT.S110484
8. Binici NC, Özyurt G. The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescent obsessive-compulsive disorder: Does comorbid anxiety disorder affect inflammatory response? Psychiatry Research, 2019; 272: 311-315. PMID: 30597382.
Doi: 10.1016/j.psychres.2018.12.131
9. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. PsychiatryResearch. Elsevier. 271(2019)131–135. PMID: 30472508.
Doi: 10.1016/j.psychres.2018.11.043
10. Sahin SK, Yasamali C, Özyürek MB, Elboga G, Altindag A, Sahin AZ. Neutrophil-lymphocyteratio in catatonia. Archive. ClinicalPsychiatry São Paulo, 2020; 47(2). Doi: https://doi.org/10.1590/0101-60830000000232
11. Balcioglu YH, Kirlioglu SS. C-Reactive Protein/Albumin and Neutrophil/Albumin Ratios as Novel Inflammatory Markers in Patients with Schizophrenia. Psychiatry Investig. 2020; 17(9): 902-910. PMID: 32894927; PMCID: PMC7538240.
12. Moosazadeh M, Maleki I, Alizadeh-Navaei R, Kheradmand M, Hedayatizadeh-Omran A, Shamshirian A, et. al. Normal values of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio among Iranian population: Results of Tabari cohort. Caspian J Intern Med. 2019 Summer; 10(3): 320-325.
13. Wei Y, Wang T, Li G, Feng J, Deng L, Xu H, et. al. Investigation of systemic immune-inflammation index, neutrophil/high-density lipoprotein ratio, lymphocyte/high-density lipoprotein ratio, and monocyte/high-density lipoprotein ratio as indicators of inflammation in patients with schizophrenia and bipolar disorder. Front Psychiatry, 2022; 26; 13: 941728. PMID: 31558995; PMCID: PMC6729162.
14. Inanli I, Aydin M, Çaliskan AM, Eren I. Neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and mean platelet volume as systemic inflammatory markers in different states of bipolar disorder. Nordic Journal of Psychiatry, 2019; 73 (6): 372-379. PMID: 31304832. Doi: 10.1080/08039488.2019.1640789
15. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Research Notes. 2017; 3; 10(1): 12. PMID: 28057051. PMCID; PMC5217256.
16. Meng X, Chang Q, Liu Y, Chen L, Wei G, Yang J, et. al. Determinant roles of gender and age on SII, PLR, NLR, LMR and MLR and their reference intervals defining in Henan, China: A posteriori and big-data-based. J ClinLab Anal. 2018; 32(2): e22228. PMID: 28378887; PMCID: PMC6817185.
17. ÖzdinSelçuk, Sarisoy G, Böke Ö. A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients – a retrospective file review, Nordic Journal of Psychiatry, 2017; 71(7): 509-512. PMID: 28644753. Doi: 10.1080/08039488.2017.1340517
18. Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, et. al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatria Danubina, 2014; 26(3): 220-5. PMID: 25191768.
19. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. BratislLekListy. 2021; 122(7): 474-488. PMID: 34161115. Doi: 10.4149/BLL_2021_078.
20. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. Scientific Reports 11, 464(2021). Doi: https://doi.org/10.1038/s41598-020-79431-7
21. Demiryürek E, Çekiç D, Işsever K, Genç AC, Yaylaci S, Demiryürek BE. Depression and Anxiety Disorders in COVID-19 Survivors: Role of Inflammatory Predictors. NoroPsikiyatrArs. 2022; 14; 59(2): 105-109. PMCID: PMC9142020.
22. Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, et. al. Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical

Cancer. Sci Rep. 2019; 1; 9(1): 3284. PMID: 30824727; PMCID: PMC6397230.
23. Dos Santos LF. Validity and reliability study of Liebowitz Social Anxiety Scale - self-applied version. Dissertation (Master of Science, area Mental Health). Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (USP) 2012. Available at: https://teses.usp.br/teses/disponiveis/17/17148/tde-03112012-112449/pt-br.php. Accessedon: 10 February 2021.
24. Caballo VE, Salazar IC, Arias V, Hofmann SG, Curtiss J. Psychometric properties of the Liebowitz Social Anxiety Scale in a large cross-cultural Spanish and Portuguese speaking sample. Braz J Psychiatry. 2019; 41(2): 122-130. PMID: 30328964; PMCID: PMC6781681
25. Rytwinski NK, Fresco DM, Heimberg RG, Coles ME, Liebowitz MR, Cissell S, Stein MB, Hofmann SG. Screening for social anxiety disorder with the self-report version of the Liebowitz Social Anxiety Scale. Depress Anxiety. 2009; 26(1): 34-8. Doi: https://doi.org/10.1002/da.20503
26. Uzun N, Akinci MA. Hemogram parameters in childhood anxiety disorders: Could anxiety disorders be related with inflammation? Medical Hypotheses. Elsevier. 2020; 110440. PMID: 33317847. Doi: 10.1016/j.mehy.2020.110440
27. Crippa J.A.S., Sanches R.F., Hallak J.E.C., Loureiro S.R., Zuardi A.W. Factor structure of Bech's version of the Brief Psychiatric Rating Scale in Brazilianpatients. Neurosciences and behavior. Braz J MedBiol Res.2002; 35(10): 1209-13. Doi: https://doi.org/10.1590/S0100-879X2002001000014
28. Crippa J.A.S., Sanches R.F., Hallak J.E.C., Loureiro S.R., Zuardi A.W. Factor structure of Bech's version of the Brief Psychiatric Rating Scale in Brazilian patients. Neurosciences and behavior. Braz J MedBiol Res.2002; 35(10): 1209-13. Doi: https://doi.org/10.1590/S0100-879X2002001000014
29. Park S-C, Eun YJ, Kiwon K, Hoseon L, Joonho C, Amitava D, et al. Establishing the cut-off scores for the severity ranges of schizophrenia on the BPRS-6 scale: findings from the REAP-AP. Psychiatry and Clinical Psychopharmacology, 2019; 29:4, 895-898. Doi: 10.1080/24750573.2019.1695994
30. Medeiros HLV de, Rocha DM, Roudig RMEW, Silva AMP da. Validated schizophrenia assessment scales for use in brazil: a systematic review. Debates in Psychiatry 2017; 7(5): 22-8. Doi: https://doi.org/10.25118/2763-9037.2017.v7.78
31. Freitas RR De. Assessment of Psychopathological Dimensions of treatment-resistant and non-treatment-resistant Schizophrenia: an international multicentercross-sectional study. Dissertation (Psychiatry Program). Universityof São Paulo Schoolof Medicine, 2018. Available at: https://www.teses.usp.br/teses/disponiveis/5/5142/tde-31102018-130536/publico/RosanaRamosdeFreitas.pdf. Accessedon: 17 February 2023.
32. Van Dorn RA, Desmarais SL, Grimm KJ, Tueller SJ, Johnson KL, Sellers BG, et. al. The latent structure of psychiatric symptoms across mental disorders as measured with the PANSS and BPRS-18. Psychiatry Res. 2016; 30; 245: 83-90. PMID: 27529666; PMCID: PMC5067208.
33. Sousa TV, Viveiros V, Chai MV, Vicente FL, Jesus G, Carnot MJ, et. al. Reliability and validity of the Portuguese version of the Generalized Anxiety Disorder (GAD-7) scale. Health Qual Life Outcomes 13,50(2015). Doi: https://doi.org/10.1590/0102-311X00212716
34. Adali MK, Buber I, Sen G, Yilmaz S. Relationship between Systemic Immune-Inflammation Index and Coronary Collateral Circulation in Patients with Chronic Total Occlusion. ArqBrasCardiol. 2022; 119(1): 69-75. PMID: 35703663; PMCID: PMC9352117. Doi: 10.36660/abc.20210414
35. Li F, Shi X, Dai C. Prognostic value of pre-operative peripheral inflammation markers in patients with squamous cell carcinoma of the external auditory canal. Brazilian Journal of Otorhinolaryngology. 2022; 88(2): 161-167. PMID: 32624372; PMCID: PMC9422596. Doi: 10.1016/j.bjorl.2020.05.018
36. Szor DJ. Evaluation of the neutrophil-lymphocyteratio as a prognostic factor in gastric cancer patients undergoing potentially curative gastrectomy. Dissertation (Doctorate of Science in Gastroenterology). University of São Paulo Schoolof Medicine, 2019. Available at: https://www.teses.usp.br/teses/disponiveis/5/5168/tde-09032020-143134/pt-br.php. Accessedon: 05 January 2021.
37. Eyff TF, Bosi HR, Toni MS, Zilio MB, Corso CO, Bersch VP, et al. The role of immunoinflammatory markers in the prognosis and resectability of pancreaticadeno carcinoma. ABCD ArqBrasCirDig. 2018; 31(2): e1366. PMID: 29972394; PMCID: PMC6044203. Doi: 10.1590/0102-672020180001e1366

Table 1: Descriptive statistics and prevalences of altered instruments and inflammation markers (blood count = CBC)

Variables	Mean ± DP ou Median (P25 – P75)	n (%)
LSAS	54 (26,8 – 86,0)	
≥ 32 points		59 (72,0)
GAD-7	7 (3 – 11)	
≥ 5 points		55 (67,1)
BPRS	21,5 (13 – 30,3)	
≥ 5 points		78 (95,1)
BLOOD COUNT		
Neutrophils	4,98 ± 2,05	
Monocytes	0,59 ± 0,21	
Lymphocytes	2,05 ± 0,76	
Platelets	215,4 ± 65,5	
Neutrophil-lymphocyteratio	2,50 (1,50 – 3,49)	
≥ 2,80		35 (42,7)
Monocyte-lymphocyteratio	0,29 (0,22 – 0,37)	
≥ 0,35		25 (30,5)
Platelet-lymphocyteratio	108,1 (82,8 – 143,5)	
≥ 362		0 (0,0)
Systemicimmune-inflammatory index	535 (303,5 – 794,2)	
≥ 761		21 (25,6)

Table 2: Correlation between the LSAS, GAD-7 and BPRS scales with the inflammation markers NLR, SII, MLR and PLR, through Spearman's correlation coefficient.

LSAS = Liebowitz Social Anxiety Scale; BRPS = Brief Psychiatric Rating Scale; GAD-7 = Generalized Anxiety Disorder Scale; NLR = Neutrophil-to-Lymphocyte Ratio; SII = Systemic Immune-Inflammatory Index; MLR = Monocyte-to-Lymphocyte Ratio; PLR = Platelet-to-Lymphocyte Ratio; rs = Spearman's correlation coefficient.

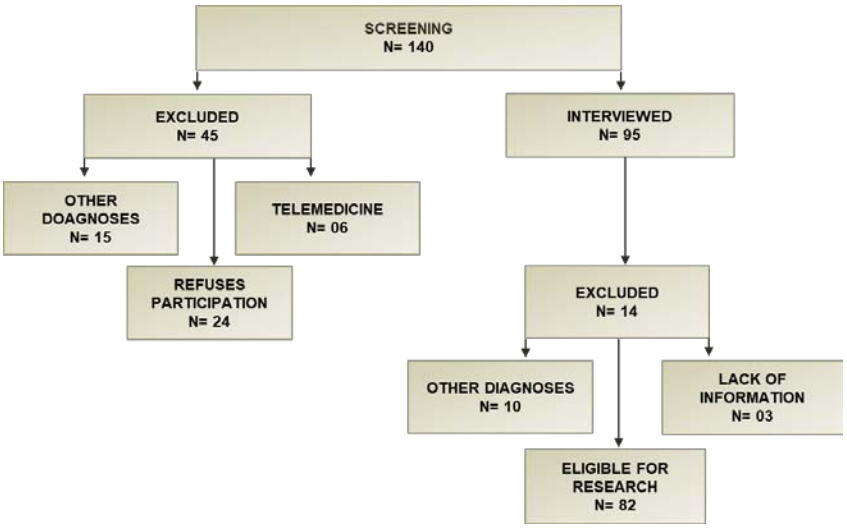
Markers of Inflammation	LSAS		GAD-7		BPRS	
	r_s	p	r_s	p	r_s	P
NLR	**0,241**	**0,029**	0,020	0,860	-0,058	0,606
SII	**0,257**	**0,020**	0,111	0,321	-0,054	0,630
MLR	0,110	0,326	-0,005	0,963	-0,043	0,702
PLR	**0,236**	**0,032**	0,112	0,318	-0,003	0,982

Table 3: Prevalence of alterations in the GAD-7 and BPRS scales and in the blood count according to the LSAS classification

Variables	No AS (n=23; 28%)	Yes AS (n=59; 72%)	P
GAD-7			
≥ 5 points	9 (39,1)	46 (78,0)	0,002
BPRS			
≥ 5 points	19 (82,6)	59 (100)	0,005
BLOOD COUNT			
Neutrophil-lymphocyteratio			
≥ 2,80	5 (21,7)	30 (50,8)	0,032
Monocyte-lymphocyteratio			
≥ 0,35	4 (17,4)	21 (35,6)	0,180
Systemicimmune-inflammatory index			
≥ 761	3 (13,0)	18 (30,5)	0,178

Table 4: Multivariate Poisson Regression Analysis to assess factors independently associated with social anxiety

Variables	Prevalence Ratio (95% CI)	P
GAD-7 ≥ 5 points	1.53 (1.04 – 2.25)	.029
BPRS		
Positive Domain	1.04 (1.01 – 1.06)	.003
Disorganized Cognitive Domain	1.04 (1.01 – 1.07)	.004
Total score	1.02 (1.01 – 1.03)	.001
Neutrophil-Lymphocyte Ratio ≥ 2,80	1.55 (1.21 – 1.98)	<.001



Source: Elaborated by the author.

Figure 1: PRISMA Flowchart: patients screened, interviewed, excluded, included, eligible.

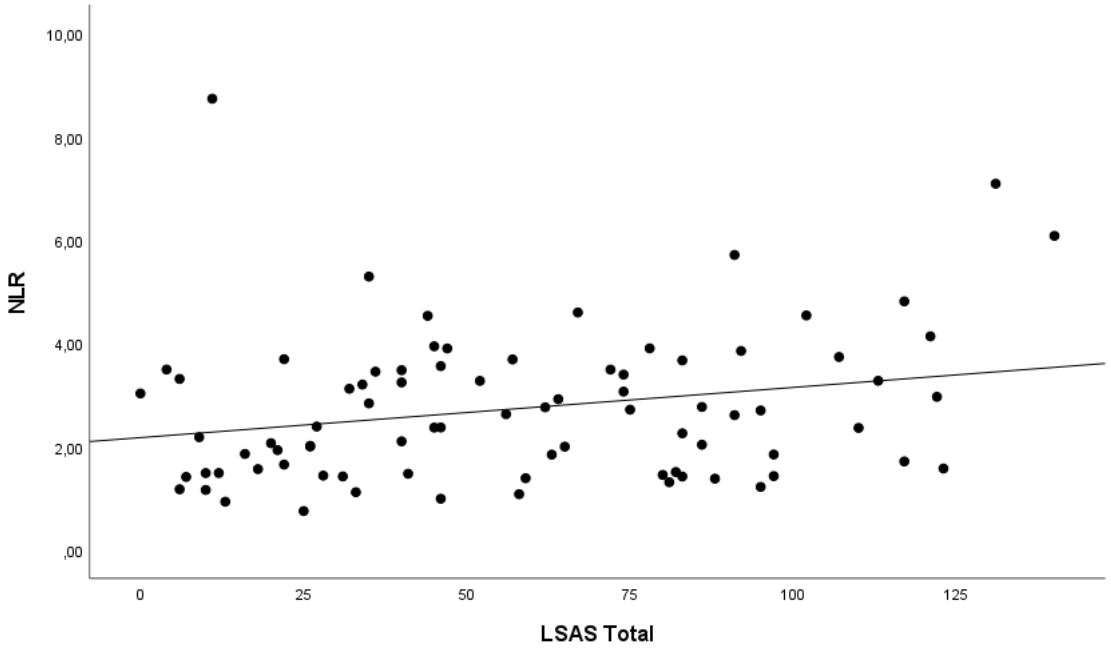


Figure 2: Scatter diagram of LSAS's correlation with NLR.

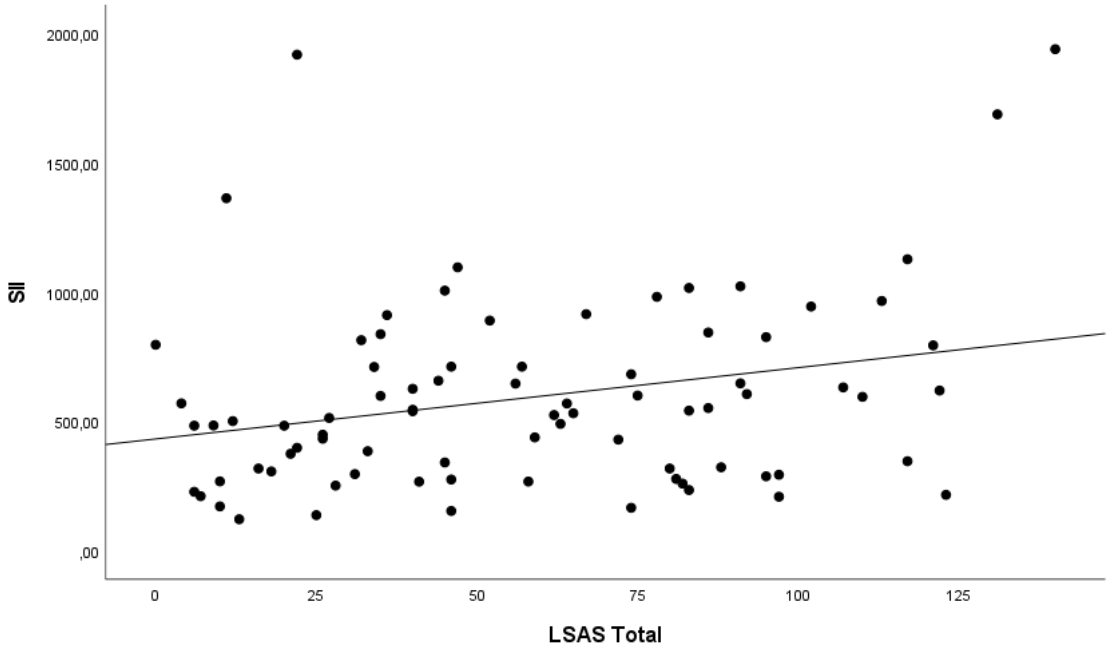


Figure 3: Scatter diagram of the LSAS correlation with SII.

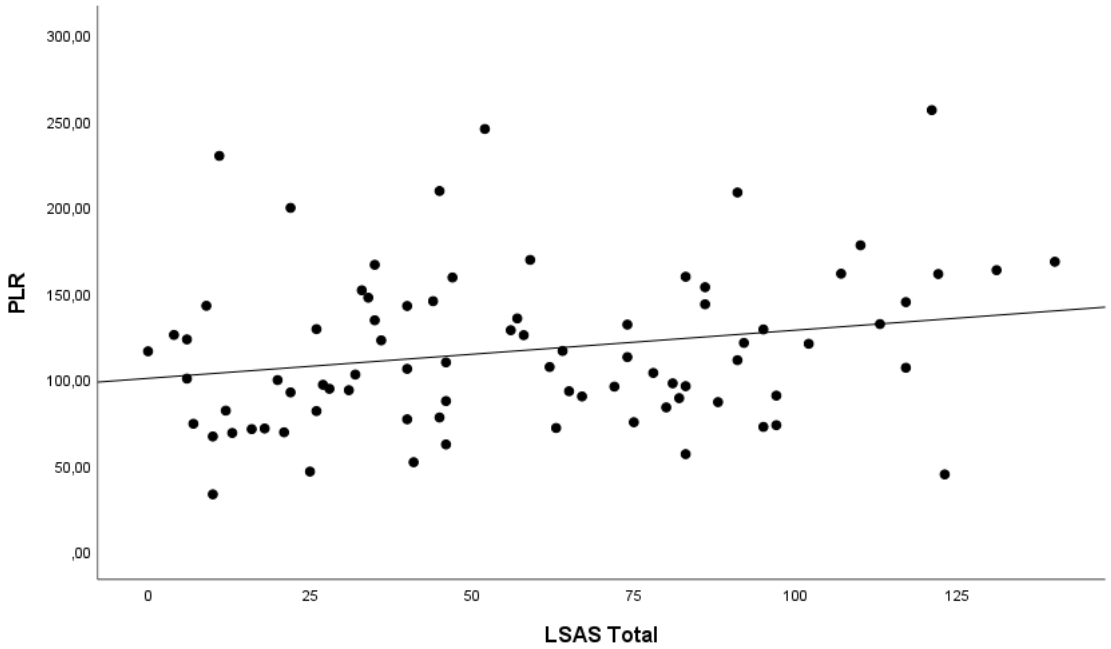


Figure 4: Scatter diagram of the correlation of LSAS with PLR.

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Cooperative, Collaborative, and Related Strategies' Effect on Learning in Children with Autism

By Dr. Özge Boşnak & Prof. Colin Calleja
Bursa Uludag University

Abstract- When the right circumstances are met, children with autism can engage in settings for general education and have a successful educational career. A truly inclusive learning environment and research-based inclusion techniques must be in place for children with autism to be successfully included. The research studies that concentrate on cooperative and collaborative learning methodologies are reviewed in this article. The article concludes by outlining the need for additional study. This study examined 29 research studies using cooperative, collaborative, and related techniques with children with autism. Each article had to meet these requirements to be included: 1. describe the use of an evidence-based intervention for at least one participant with ASD. 2. Consist of at least one collaborative, cooperative, or related method. 3. Research needed to be conducted in an inclusive setting and finally, 4. The reviewed articles had to have been released in 2010 or later.

Keywords: inclusion, cooperative learning, collaborative learning, children with autism.

GJMR-A Classification: NLMC Code: WL 352

Cooperative, Collaborative, and Related Strategies' Effect on Learning in Children with Autism

Dr. Özge Boşnak [1] & Prof. Colin Calleja [2]

Abstract- When the right circumstances are met, children with autism can engage in settings for general education and have a successful educational career. A truly inclusive learning environment and research-based inclusion techniques must be in place for children with autism to be successfully included. The research studies that concentrate on cooperative and collaborative learning methodologies are reviewed in this article. The article concludes by outlining the need for additional study. This study examined 29 research studies using cooperative, collaborative, and related techniques with children with autism. Each article had to meet these requirements to be included: 1. describe the use of an evidence-based intervention for at least one participant with ASD. 2. Consist of at least one collaborative, cooperative, or related method. 3. Research needed to be conducted in an inclusive setting and finally, 4. The reviewed articles had to have been released in 2010 or later.

Keywords: inclusion, cooperative learning, collaborative learning, children with autism.

I. Introduction

Autism, a neurodevelopmental disorder, significantly influences an individual's daily life, impeding their ability to engage in typical activities, particularly in the realms of social interaction and communication. It manifests in restrictive behaviours, often characterized by repetitive actions, which encompass stereotypy, ritualistic behaviour, perseveration (Ringdahl, 2011), and compulsions. (American Psychatric Association, 2013)

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), autism is a spectrum disorder with varying degrees of severity and presentation. The core symptoms of autism are evident early in childhood and persist throughout the individual's lifespan. One can observe repetitive behaviours and fixation on particular interests and, or specific activities.

The authors of this paper maintain the belief that it is possible for children on the autism spectrum to receive education alongside their same-age peers in mainstream schools. Specific adaptations will be needed. Lindsay (2007) pointsout that inclusion is a crucial education plan designed to increase the educational opportunities of students with particular needs.

Author 1: Bursa Uludag University, Education Faculty, Special Education Department.
Author 2: University of Malta, Faculty of Education, Department for Inclusion and Access to Education. e-mail: colin.calleja@um.edu.mt

Research such as that carried out by Crosland and Dunlap (2012) and Sanahuja and Qinyi (2012) has shown that students with autism spectrum disorders (ASD) benefit from attending mainstream, although additional support is required. This paper reviews individualized and systemic interventions, specifically cooperative learning strategies, used with autistic children. These strategies are believed to help create an inclusive learning environment. Therefore, in this paper, we discuss strategies for the successful inclusion of children with autism, which can be used by educators in mainstream environments.

II. Method

a) Search Procedures

The studies in this research were obtained by searching research papers in the HyDi database, which discuss cooperative and collaborative strategies. HyDi is an extensive database with access rights to many databases such as Education Database, Web of Science, ProQuest Central, Social Science Database, Springer, and EBSCOhost.

The terms "cooperative," "collaborative," and "learning strategies" were employed in conjunction with "autism," "Asperger," and "inclusion.". The returned papers were sorted by relevance, and the abstracts of all articles containing "autism" or "Asperger" in the title were manually screened. Publications that did not pertain to the research question of the current study, meaning they contained the search terms in a different context, were excluded. The search also included papers that were cited in the articles which were selected for inclusion. Studies published between 2010 and the spring of 2023 were included in this literature review. The literature searches were conducted in the winter of 2022 and again in the spring of 2023.

The Web of Science allowed us to refine our search results by choosing pertinent research areas. We utilized this function by selecting "education-educational research." Within this database, the search yielded 102 papers, of which 8 met the inclusion criteria. EBSCO Host provided the option to search several databases. This search returned 113 papers, with six qualifying for inclusion. ProQuest Central provided the option to narrow down the search result by title; we selected autism or Asperger's. This search returned 82 papers, of which eight qualified for review. Social Science Database produced 22 papers, four qualifying for

inclusion. Springer returned 18 papers, and one qualified for review. Education Database produced 49 papers, two qualifying for inclusion. All abstracts were read, and 29 articles were selected for review.

b) Inclusion and Exclusion Criteria

For inclusion in this extensive review, each article underwent evaluation based on several criteria. Initially, the article needed to detail the application of an evidence-based intervention for at least one participant with ASD. Secondly, the articles were required to incorporate a minimum of one cooperative learning strategy. Thirdly, the research was mandated to have been conducted within an inclusive setting. Lastly, the reviewed articles were expected to have been published in the year 2010 or later.

III. Results

a) Review of Strategy 1: Cooperative group teaching

Cooperative learning is one of the methods that enable students with disabilities to reveal their strengths and weaknesses together with their typically developing peers (Corbett et al., 2013). Studies on cooperative learning have shown that it positively affects the social acceptance of students with disabilities in general education classes (Gilles, 2007). Supporters of the cooperative learning model believe that learning consists of various components. Cooperative learning is a very beneficial model for children with autism. Corbett et al., (2013) emphasized that Student Team Learning (STL) has three bases. These are team rewards, individual responsibility, and equal opportunities for success. Using STL techniques, teams earn certificates or other team rewards if they exceed a designated criterion. Personal accountability implies that the team's overall success relies on the individual learning efforts of all team members. This redirects the team members' actions towards elucidating concepts to their peers and ensuring that everyone in the team is adequately prepared for quizzes or assessments, which they must undertake independently, without reliance on their teammates. Equal opportunities for success mean that students contribute to their teams by improving over their past performances. This ensures that high, average, and low achievers are equally challenged to do their best and that the contributions of all team members will be valued.

Cooperative learning is a method that can foster success for future generations. The SENSE Theatre project, a peer-mediated initiative immersed in play and focused on performance, is introduced by Corbett et al. (2013). Through the programme, actors of a similar age who are ordinarily developing are paired with individuals who have Autism Spectrum Disorder (ASD) to serve as co-actors and peer models in a play. The severity of each participant's symptom profile and their prior interaction with the ASD community are taken into consideration during the matching process. Ten main goals are the emphasis of the SENSE Theatre approach. These goals are communicated, exemplified, and integrated through direct instruction, bolstered by a variety of case studies and ongoing, supervised experience.

These ten main goals are clearly explained to peers and are intended to improve different facets of autism symptomology. The primary goals and desired behaviours include: (1) giving social support to establish trust and lower stress levels; (2) making an enjoyable environment to promote social play; (3) modeling warm social interaction to encourage reciprocal engagement with peers; (4) increasing motivation to boost social initiation; (5) using directed communication to improve verbal back-and-forth conversation; (6) using nonverbal communication to enhance gestures, eye contact, and facial expressions; (7) playing imaginatively to cultivate creativity; (8) using empathic responding to foster empathy; 9) supporting active learning to promote novelty and participation; and (10) advancing individual learning by combining social learning with behaviour.

Studies on this subject are summarized in Table 1.

Table 1: Cooperative Learning articles, empirical studies

Author(s), year	Sample	Age	Design	Intervention	Findings
Cheng and Ye, 2010	1 girl, 2 boys	7-8 y	Multiple probe design across participants	Social competence in a collaborative virtual environment	The results showed that using the CVLE-social interaction system had significant positive effects on participants' performance, both within the CVLE-social interaction system and in terms of reciprocal social interaction learning.
Lee, et al., 2021	3 boys ASD	4-5y	Multiple probe design across participants	Physical Activities	Although the frequency of inappropriate interactions increased after the intervention in both settings, the proportion of inappropriate interactions relative

				to appropriate interactions decreased for two children in the PE setting and for all three children in the free-play setting
Scott, 2019	3 boy, 1 girl with 5 fifth grade peers	10-11 y	ABA	Hidden Curriculum of group work	Results from this study indicate that when the four participants with ASD used a structured protocol that guided communication attempts (through explicit tasks) during cooperative academic group work their overall interaction attempts increased, as did their (prompted and unprompted) reciprocal exchanges.

All the studies reviewed here were designed with a single-subject experimental model. A total of 15 students, 13 of whom were ASD students (n = 13 ASD), were included in the studies. Participants were between the ages of 4 and 11. These studies were carried out in inclusive environments, in preschool, primary, and secondary schools. A variety of behaviours were targeted for intervention. In one study (Cheng & Ye, 2010), the focus was on enhancing social competence in a collaborative virtual environment. Another study (Scott, 2019) delved into the hidden aspects of group work's curriculum, while Lee et al. (2021) concentrated on physical activities.

Cheng and Ye (2010) focus on using a virtual learning environment to help the deficiencies of social competence for people with ASDs and to increase their social interaction. In particular, it provides a basic exploration of social competence within collaborative virtual learning environment (CVLE) systems and behavioural performance in social and cognitive interactions. Thus, this CVLE-social interaction system involves a 3D expressive avatar, an animated social situation, with verbal and text communication. The results showed that using the CVLE-social interaction system had significant positive effects on participants' performance, both within the CVLE-social interaction system and in terms of reciprocal social interaction learning.

Lee et al., (2021) evaluated the effects of cooperative physical activities on the social interactions of children with autism spectrum disorder (ASD) in China. Cooperative physical activities include procedures such as peer selection, peer practice, group task completion, and an interdependent group contingency. The intervention took place during inclusive physical education (PE) classes. The generalization of interactions with peers was evaluated during free play. Although the frequency of inappropriate interactions increased after the intervention in both settings, the proportion of inappropriate interactions relative to appropriate interactions decreased for two children in the PE setting and all three children in the free-play setting.

Scott (2019) used Video-recorded observations. The observations were transcribed and coded according to the nature of each conversational attempt, which included prompted reciprocal communication, unprompted reciprocal communication, self-centric conversations, directives, clarification questions/ statements, and off-topic remarks. Results from this study indicate that when the four participants with ASD used a structured protocol that guided communication attempts (through explicit tasks) during cooperative academic group works, their interaction attempts increased, as did their (prompted and unprompted) reciprocal exchanges.

b) Review of Strategy 2: Peer Tutoring and Peer Influences

Peer-mediated instruction is implemented by pairing a child on the spectrum with another child without disabilities (Berman, 2019). Thus, rather than involving just a teacher or therapist through this strategy, one or more peers will take on a role in the teaching/learning process. This intervention can be used in small groups and classroom-wide intervention programs (Zhang et al.2022). Research has indicated that peer-mediated instruction and interventions are effective because they create more chances for individuals to practice proper social and communication skills during natural interactions with others (Schmidt & Stichter, 2012). If properly designed and implemented, peer support strategies can be a valuable method for providing academic and social support to students with disabilities (Bell & Carter, 2013). Peer support strategies refer to a wide variety of intervention approaches. The main three approaches are (a) classroom-wide peer tutoring, (b) peer support arrangements, and (c) lunch bunches.

Classroom-Wide Tutoring consists of dividing the class into diverse small learning groups. Teams should include at least one high-performing student, an average student, and an underperforming student with a disability (Lundblom & Woods, 2012). Thus, while there is heterogeneity within groups, groups are similar across the class, allowing the educator to capitalize on the groups' complementary knowledge and achieve higher-level, collaborative objectives. The teacher conveys to students that every team collectively bears the responsibility of aiding all its members in comprehending the material taught earlier. Teammates should have the chance to collaborate in problem-solving or grasping the content, with each potentially taking on the role of the designated "tutor" within the group (Lundblom & Woods, 2012).

Peer Support Arrangements involve equipping one or more general education students in an inclusive classroom to provide academic and social support to students with disabilities (Corbett et al., 2013). Broad descriptions of individualized educational objectives, participation objectives, and social interaction objectives for the student with a disability are shared with the peers. Educators with expertise in special education or paraprofessionals offer comprehensive support to facilitate the peer counseling process and assist students in achieving their established objectives (Corbett et al., 2013).

Lunch Bunches relates a student with a disability to a group of students without similar disabilities or students without disabilities to join them for lunch, focusing on social interaction during that lunchtime (Fan et al., 2021). Prior to becoming part of the group, typical education students undergo social skills training. This training encompasses demonstrations of the social skills that the strategy will highlight, role-playing, and explicit instruction in those skills. Alongside engaging in asking and answering questions with one another, students can also take turns discussing various topics of interest to the group.

Studies conducted in this field since 2010 are summarized in Table 2.

Table 2: Peer tutoring and Peer influence articles

Author(s), year	Sample	Age	Design	Intervention	Findings
Banda., and Hart., 2010	2 girls with ASD	8 y	Multiple baseline designs across participants	Peer-to-peer social skills through direct instruction	Results indicated increased social initiations in both participants and sharing behaviours in one of the participants, but no increases in responses in both participants.
Berman., 2019	2 boys with ASD and 5 peers of the same ages	4 y	ABAB model	Group Affection Activities (GAA) on social interaction	The findings agree with those reported by previously conducted studies, however, the maintenance and generalization of improved interaction skills remain to be of great concern. It is suggested that in order to address this important issue, an intervention program combining Group Affection Activities with peer training should be systematically integrated into the early childhood curriculum and implemented for all to benefit.
Collet-Klingenberg., Neitzel., and LaBerge., 2012	3 boys, 1 girl with ASD, and 18 peers	12-13 y	Pre-test Post-test	Power-PALS (Peer Assisting,Leading, Supporting) Implementing a peer-mediated intervention	Power Pals had a significant impact on school experiences and social interactions for both learners with and without ASD.

Corbett et al., 2013	9 boys, 3 girls with ASD, and K-12 school peers	8-17 y	Pre-test post-test	Behavioural strategies and theatrical techniques in a peer-mediated model	The investigation of the SENSE Theatre peer-mediated, interactive social skills program corroborates showing improvement in core social deficits in ASD using a short-term, summer camp model that allows the extensive practice of social interactions with peers.
Fan et al., 2021	1 boy with ASD	9 y	Case study	Peer engagement and interaction in summer camps	Peer engagement and reciprocal interactions improved following the disclosure protocol and continued to improve on the final day of the camp, which was not observed in the non-disclosure camp. A key qualitative theme revealed that changed behavioural attribution was the main contributor to improved inclusion following disclosure.
Ganz et al., 2012	1 girl with ASD and 2 peers	15 y	Multiple baseline design across communication responses	Visual scripts on social and communication skills	The target student demonstrated improve-ments in three communicative behave-ours when implemented by a trained peer; however, behaviours did not generalise to use with an untrained typically developing peer
Gardner et al., 2014	2 boys with ASD and 10^{th}-12^{th} grade 2 boys 4 girls peers	14-18 y	ABAB and ABA withdrawal design	Peer network intervention	We examined peer networks as a promising strategy for increasing the opportunities students with ASD have to interact with and strengthen social skills among classmates without disabilities.
Hochman et al., 2015	4 boys with ASD and 2 typically developed girls' peers	15-17 y	Multiple baseline designs across participants	Peer network strategies on the social engagement	Substantial increases in the percentage of intervals containing peer interactions and social engagement across all participants.
Krebs., McDaniel., and Neeley, 2010	2 children with ASD and 1 girl, and 3 boys peers at the same ages		Multiple probe design across task replicated across participants	Peer training intervention on social interactions	Data collected indicated that peer training of targeted social interaction behaviours resulted in increased use of target behaviours by participants with ASD. Unexpectedly, results also indicated an increase in social behaviours that had not

					been targeted to be elicited by peers during the interaction.
Ledbetter-Cho et al, 2015	3 boys with ASD and 3 siblings	4-6 y	Multiple baseline designs across participants	Effects of a script-training procedure on the peer-to-peer communication of 3 children with ASD during group play with peers.	The results of this study replicate and extend previous research on the use of script training to improve the peer-to-peer communications of children with ASD. Participants rarely spoke to each other during the baseline, but with the introduction of scripts, each participant peer to peer communication improved.
Lundblom., and Woods., 2012	4 girls with ASD	12 y	Multiple baseline design	Improving idiom comprehension	Response to intervention provides a framework to implement a classroom intervention for all students to facilitate idiom understanding.
Oppenheim-Leaf., 2012	3 boys with typically developed and their siblings with ASD	4-6 y	A multiple probe design across skills replicated across participants	Social play	All three typically developing children learned the targeted skills during role-plays with a teacher and, to a large part, generalized the skills when they played with their brothers with autism. In addition, some children who learned these skills increased their positive interactions and decreased negative interactions during a free-play period with their sibling with autism.
Parsons., Cordier., Munro., and Joosten., 2019	62 children with ASD and 62 peers	6-11 y	Quantitative Methods	Peer-mediated, play-based intervention	A peer-mediated, play-based intervention was effective in improving pragmatic language performance in children with autism aged 6–11 years.
Radley et all., 2017	3 boys with ASD and 2 peers	5 y	Multiple probe design	Effects of the Superheroes Social Skills program	Participants with ASD demonstrated increases in the level and trend of target skill accuracy from baseline to intervention phases in the training set, with NAP (Nonoverlap of All Pairs) scores ranging from moderate to strong effects.
Schmidt., and Stichter., 2012	3 boys with ASD and 2 boys, 1 girl peers	12-13 y	Multiple treatments design (ABCDCD)	Peer mediated intervention	The results indicate that the addition of peer-mediated interventions enhanced generalized gains in social interaction beyond those of a

					school-based social competence intervention.
Sreckovic., Hume and Able., 2017	3 boys with ASD and 9th – 11th grade 14 peers		Multiple baseline designs across participants	Peer network intervention	Results indicate peer networks are effective at increasing social interactions of secondary students with ASD and provide preliminary support for the use of peer networks to reduce rates of bullying victimization.
Trottier, N., Kamp, L., and Mirenda, P., 2011	2 boys with ASD and 6 peers	11 y	Multiple Baseline Design	Peer-mediated intervention designed to teach two students with ASD to use speech-generating devices (SGDs) to engage in interactions with peers in a social context at school.	Results provide evidence that the confederates acquired the skills needed to support SGD use by students with ASD. The results also suggest that the intervention was effective at increasing total appropriate CAs by students with ASD. In addition, social validity ratings by all of the confederates were positive.
Zhang et al., 2022	110 children with ASD and 16 peers	4-12 y	Single-blind and parallel-controlled design	Peer-mediated intervention on social skills	PMI therapy can increase social motivation in children with mild to moderate ASD, minimize undesirable behaviour patterns, effectively improve overall social skills and enhance effective social communication with others.

A total of 241 autistic persons participated in these investigations, according to an overall analysis of the trials. Examining the participants' gender characteristics reveals that 47 of them are male and 15 are female. Furthermore, the gender of 179 people with autism was not identified. There are 15 boys and 15 girls among children with typical development. The 134 students' genders were not identified. This group, along with their peers, constituted the 375 participants in the study. The age range spans from 4 to 18.

When the methods of the studies are examined, it is noticeable that most of them are carried out with a single-subject design. Seven of them used multiple baselines (Banda., et al., 2010; Ganz., et al., 2012; Hochman., et al., 2015; Ledbetter-Cho., et al., 2015; Lundblom., & Woods, 2012; Sreckovic., et al.,2017; Trottier., et al., 2011), three of them used multiple probes (Krebs., et al.,2010; Oppenheim-Leaf., et al., 2012; Radley et al., 2017) and three of them used withdrawal design (Berman, 2019; Gardner et al., 2014; Schmidt., & Sticher, 2012). The other two studies used quasi-experimental designs (Collect-Klingenberg, et al., 2012; Corbett., et al., 2013), and one study used quantitative methods (Parsons., et al., 2019). The other one study used qualitative methods (Fan et al., 2021), and yet another used clinical trials (Zhang et al., 2022).

When we examine the type of intervention the studies used one would see that most used social skills and social instruction (Banda., et al., 2010; Berman, 2019; Corbett., et al., 2013; Fan et al., 2021; Ganz et al., 2012; Krebs., et al., 2010; Ledbetter-Cho., et al., 2015; Oppenheim-Leaf., et al., 2012; Parsons., et al., 2019; Radley et al., 2017; Schmidt., & Sticher, 2012; Trottier., et al., 2011; Zang et al., 2022). Only a few of them used peer networks (Becevic et al., 2021; Gardner et al., 2014; Hochman et al., 2015; Sreckovic., et al., 2017).

c) Review of Strategy 3: Social Skills Training

Individuals with autism spectrum disorders (ASD) have recently received a lot of attention both within and outside the PBS (Positive Behaviour Support) community (Vincent et al., 2022). Because social interaction is a common problem for people on the spectrum, many social skills interventions have been designed to try to improve the social aspects of their

lives (Corbett., et al.,2013). Although there is increasing evidence supporting the use of social skills training to improve social performance, there is little evidence that this enhanced performance improves the quality of social life of people with ASD (McMahon, et al., 2012). This discrepancy is, at least in part, due to how the dependent variable was defined. Researchers commonly evaluate the efficacy of interventions by examining observable changes in behaviour, focusing on the behaviour's outward appearance. Examples of these dependent variables encompass aspects like social initiation, social response, conversational skills, and peer imitation (Sabey et al., 2020). As a majority of studies within this category revolve around peer interactions, they were primarily assessed under the former title. Upon evaluating the studies, it becomes evident that a total of 140 individuals with autism were involved in the research. Regarding the gender composition of the participants, five were male, two were female, and the gender of 133 individuals with autism was not specified. The age range of the participants varied from 6 to 12 years. If the methods of the studies are examined, one can notice that different designs were used. For instance, Kasari et al. (2012) employed a 2x2 factorial design, McMahon et al. (2012) utilized a clinic-based intervention approach, Sabey et al. (2020) incorporated both observational and interventional design, Sansi et al. (2021) employed a mixed-method sequential exoplanetary design, and Vincent, et al. (2022) adopted a single-case experimental design.

All the interventions evaluated used social skills intervention, but they used different programs such as peer social connection (Kasari, et al., 2012), vocalizations (McMahon, et al., 2012), social behaviour (Sabey, et al., 2020), physical activity (Sansi, et al., 2021), and cooperative play (Vincent et al., 2022).

Table 3: Social skills training articles

Author(s), year	Sample	Age	Design	Intervention	Findings
Kasari., Rotheram-Fuller., Locke and Gulsurd., 2012	60 students with ASD	8 y	2 x 2 factorial design	Social Skills	Significant improvements can be made in peer social connections for children with autism spectrum disorders in general education classrooms with a brief intervention, and these gains persist over time.
McMahon., Vismara., and Solomon, 2012	28 students with ASD	12 y	Clinic-based intervention	Social Skills Training	Over the course of the intervention, participants made fewer initiating and other vocalizations, more responding vocalizations, spent more time interacting with a group of peers and spent marginally less time interacting with a leader.
Sabey., Ross., and Goodman, 2020	2 boys, and 1 girl with ASD	7-11 y	Observational and interventional design	Social skill training	The intervention increased participants' social behaviour. However, its mixed results in the quality of peer responses may be a more meaningful indicator of its effect on the quality of social lives of the participants.
Sansi., Nalbant., and Ozer, 2021	45 students with ASD	6-11 y	Mixed-method sequential exoplanetary design	Physical Activity Program on the motor skills, social skills	The IPA program increased the motor and social skills of ASD students.
Vincent et al., 2022	3 boys, 1 girl with ASD	6-8 y	Single-case experimental design	Social Skills Intervention	The students on the autism spectrum showed increases in the percentage of time engaged in cooperative play with peers during the intervention.

d) Review of Strategy 4: Collaborative Teaching

Schools are communal organizations, and for teachers, collaborative competence is an essential component of their expertise. Similarly, Collaboration is an essential aspect of teacher education, helping students learn how to teach effectively and develop their team teaching (Huskens, et al, 2014).

Collaborative learning focuses on five key characteristics (DatTran, 2013). The five pillars of collaborative learning theory are consistent with the

concept of collaboration and include Positive Interdependence, Direct Interaction, Individual Accountability, Group Handling, and Interpersonal and Small Group Skills. All of these give teachers the power to get involved and participate in the educational process. Each of the five components of co-learning theory articulates the social context of collaborative teaching in the classroom and the expected role of all group members.

Studies conducted in this field concerning ASD students since 2010 are summarized in Table 4.

Table 4: Collaborative teaching articles

Author(s), year	Sample	Age	Design	Intervention	Findings
Becevic., et all., 2021	490 students with ASD	?	Cross-sectional post-virtual clinic surveys	Virtual Collaborating	Participants reported an increase in self-efficacy in identifying ASD symptoms in children, assessing medical comorbidities, and learning new information.
Huskens., et al., 2014	3 boys with ASD and their siblings	5-13 y	Multiple baseline design across three child siblings' pairs	Robot-mediated intervention on improving collaborative behaviours	The robot intervention resulted in no statistically significant changes in the collaborative behaviours of the children with ASD. Despite the limited effectiveness of the intervention, this study provides several practical implications and directions for future research.
Lehane., and Senior., 2020	3 boys with ASD	9-10 y	Mixed-methods design	Collaborative teaching	Based on these preliminary results, co-teaching appears to be an effective mode of instruction for meeting the needs of pupils with, and without, SEN in mainstream settings.

Upon review of the studies, it is evident that a cumulative total of 496 individuals with autism were participants in these research endeavours. When the gender characteristics of the participants are examined, it is seen that 6 of them are boys, and the gender of 490 individuals with autism was not specified. The age ranges vary between 5 and 13 years old.

Different types of designs were used in these studies. Becevic et al. (2021) employed a cross-sectional post-virtual clinic survey design, Huskens, et al. (2014) utilized a multiple baseline design, and Lehane and Senior, (2019) incorporated a mixed-methods approach. Upon evaluation of the interventions, it is apparent that all of them were based on collaborative learning and teaching methods.

All the interventions evaluated used different programs such as virtual collaboration (Becevic, et al., 2021), robot-mediated intervention (Huskens, et al., 2014), and collaborative teaching (Lehane & Senior, 2020).

IV. Conclusion

This review has shown that cooperative learning strategies enable students with disabilities to share their skills and weaknesses with their peers who are typically developing (Corbett et al., 2013). According to studies on cooperative learning, it helps general education students with impairments feel more accepted by their peers. (Gilles, 2007). Cooperative and collaborative learning proponents, as shown in the reviewed studies, hold that cooperative learning is a particularly useful strategy for children with autism.

Collaborative work among students, aimed at achieving a common goal, often leads to increased success and productivity compared to individual efforts. Creating learning environments that foster positive interdependence is generally more favorable than those emphasizing independence. It's widely recognized that student cooperation within groups can be challenging, and it's important to establish groups in a way that makes the five essential elements of successful collaboration clear. These elements include promoting productive interactions among group members, ensuring individual accountability, explicitly teaching necessary social skills, and encouraging groups to reflect on both task management and interpersonal interactions.

When these key components are integrated into group work, students are more likely to feel motivated to work together to attain both their individual and the group's objectives. They become more inclined to take personal responsibility for their contributions to the group and their interactions with fellow group members. They also tend to show greater respect for the contributions of others and are committed to resolving disagreements democratically. Moreover, they actively

contribute to effective task management and the maintenance of positive working relationships.

References Références Referencias

1. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596
2. Banda, D. R., & Hart, S. L. (2010, June). Increasing peer-to-peer social skills through direct instruction of two elementary school girls with autism. Journal of Research in Special Educational Needs, 10(2), 124–132. https://doi.org/10.1111/j.1471-3802.2010.01149.x
3. Becevic, M., Nair, P., Wallach, E., Hoffman, K., & Sohl, K. (2021, January). ECHO Autism: Evaluation of Participants' Perceptions of Collaborative Telementoring Network. Journal of Patient Experience, 8, 237437352110652. https://doi.org/10.1177/23743735211065292
4. Bell, L., & Carter, E. W. (2013). Peer-mediated support strategies. Tennessee Department of Education. Retrieved from https://vkc.mc.Vanderbilt.edu/assets/files/resources/psiPeermedstrategies.pdf
5. Berman, Z. (2019, January 2). Increasing the Social Interaction of Two Children with Autism Spectrum Disorder and Their Peers. International Journal of Early Childhood Special Education, 10(2), 62–74. https://doi.org/10.20489/intjecse.506844
6. Cheng, Y., & Ye, J. (2010, May). Exploring the social competence of students with autism spectrum conditions in a collaborative virtual learning environment – The pilot study. Computers & Education, 54(4), 1068–1077. https://doi.org/10.1016/j.compedu.2009.10.011
7. Collet-Klingenberg, L., Neitzel, J., &Laberge, J. (2012, June). Power-PALS (Peers Assisting, Leading, Supporting): Implementing a Peer-Mediated Intervention in a Rural Middle School Program. Rural Special Education Quarterly, 31(2), 3–11. https://doi.org/10.1177/875687051203100202
8. Corbett, B. A., Swain, D. M., Coke, C., Simon, D., Newsom, C., Houchins-Juarez, N., Jenson, A., Wang, L., & Song, Y. (2013, October 22). Improvement in Social Deficits in Autism Spectrum Disorders Using a Theatre-Based, Peer-Mediated Intervention. Autism Research, 7(1), 4–16. https://doi.org/10.1002/aur.1341
9. Crosland, K., & Dunlap, G. (2012). Effective Strategies for the Inclusion of Children with Autism in General Education Classrooms. Behavior Modification, 36(3), 251–269. https://doi.org/10.1177/0145445512442682
10. Fan, L., Shire, S., Couture, M., Zwaigenbaum, L., & Thompson-Hodgetts, S. (2021, March 26). The influence of disclosure of an autism diagnosis on peer engagement and interactions for a child with autism in summer camps: a case study. Disability and Rehabilitation, 44(16), 4519–4530. https://doi.org/10.1080/09638288.2021.1904012
11. Ganz, J. B., Heath, A. K., Lund, E. M., Camargo, S. P. H., Rispoli, M. J., Boles, M., & Plaisance, L. (2012, May). Effects of Peer-Mediated Implementation of Visual Scripts in Middle School. Behavior Modification, 36(3), 378–398. https://doi.org/10.1177/0145445512442214
12. Gardner, K. F., Carter, E. W., Gustafson, J. R., Hochman, J. M., Harvey, M. N., Mullins, T. S., & Fan, H. (2014, June). Effects of Peer Networks on the Social Interactions of High School Students with Autism Spectrum Disorders. Research and Practice for Persons with Severe Disabilities, 39(2), 100–118. https://doi.org/10.1177/1540796914544550
13. Gillies, R. (2007). Cooperative Learning: Integrating Theory and Practice. Sage Publications 10.4135/9781483329598.
14. Hochman, J. M., Carter, E. W., Bottema-Beutel, K., Harvey, M. N., & Gustafson, J. R. (2015, May 21). Efficacy of Peer Networks to Increase Social Connections among High School Students with and Without Autism Spectrum Disorder. Exceptional Children, 82(1), 96–116. https://doi.org/10.1177/0014402915585482
15. Huskens, B., Palmen, A., Van der Werff, M., Lourens, T., & Barakova, E. (2014, November 28). Improving Collaborative Play Between Children with Autism Spectrum Disorders and Their Siblings: The Effectiveness of a Robot-Mediated Intervention Based on Lego® Therapy. Journal of Autism and Developmental Disorders, 45(11), 3746–3755. https://doi.org/10.1007/s10803-014-2326-0
16. Kasari, C., Rotheram-Fuller, E., Locke, J., & Gulsrud, A. (2011, November 26). Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. Journal of Child Psychology and Psychiatry, 53(4), 431–439. https://doi.org/10.1111/j.1469-7610.2011.02493.x
17. Krebs, Mcdaniel, & Neeley. (2010). The Effects of Peer Training on The Social Interactions of Children with Autism Spectrum Disorders. Education, 131(2), 393–403.
18. Ledbetter-Cho, K., Lang, R., Davenport, K., Moore, M., Lee, A., Howell, A., Drew, C., Dawson, D., Charlop, M. H., Falcomata, T., & O'Reilly, M. (2015, August 24). Effects of script training on the peer-to-peer communication of children with autism spectrum disorder. Journal of Applied Behavior Analysis, 48(4), 785–799. https://doi.org/10.1002/jaba.240
19. Lee, G. T., He, L., & Xu, S. (2021, September 7). Using Cooperative Physical Activities in Inclusive

Settings to Enhance Social Interactions for Pre-schoolerswith Autism Spectrum Disorder in China. Journal of Positive Behavior Interventions, 24(3), 236–249. https://doi.org/10.1177/10983007211035135
20. Lehane, P., & Senior, J. (2019, August 12). Collaborative teaching: exploring the impact of co-teaching practices on the numeracy attainment of pupils with and without special educational needs. European Journal of Special Needs Education, 35(3), 303–317. https://doi.org/10.1080/08856257.2019.1652439
21. Lindsay, G. (2007). Educational Psychology and the Effectiveness of Inclusive Education/Mainstreaming. British Journal of Educational Psychology, 77, 1-24. https://doi.org/10.1348/000709906X156881
22. Lundblom, E. E. G., & Woods, J. J. (2012, February 17). Working in the Classroom. Communication Disorders Quarterly, 33(4), 202–219. https://doi.org/10.1177/1525740111404927
23. McMahon, C. M., Vismara, L. A., & Solomon, M. (2012, December 14). Measuring Changes in Social Behavior During a Social Skills Intervention for Higher-Functioning Children and Adolescents with Autism Spectrum Disorder. Journal of Autism and Developmental Disorders, 43(8), 1843–1856. https://doi.org/10.1007/s10803-012-1733-3
24. Oppenheim-Leaf, M. L., Leaf, J. B., Dozier, C., Sheldon, J. B., & Sherman, J. A. (2012, April). Teaching typically developing children to promote social play with their siblings with autism. Research in Autism Spectrum Disorders, 6(2), 777–791. https://doi.org/10.1016/j.rasd.2011.10.010
25. Parsons, L., Cordier, R., Munro, N., & Joosten, A. (2019, August 27). A Randomized Controlled Trial of a Play-Based, Peer-Mediated Pragmatic Language Intervention for Children with Autism. Frontiers in Psychology, 10. https://doi.org/10.3389/fpsyg.2019.01960
26. Radley, K. C., O'Handley, R. D., Battaglia, A. A., Lum, J. D. K., Dadakhodjaeva, K., Ford, W. B., & McHugh, M. B. (2017). Effects of a Social Skills Intervention on Children with Autism Spectrum Disorder and Peers with Shared Deficits. Education and Treatment of Children, 40(2), 233–262. https://doi.org/10.1353/etc.2017.0011
27. Ringdahl, J.E. (2011). Rituals, Stereotypies, and Obsessive-Compulsive Behavior. In: Matson, J., Sturmey, P. (eds) International Handbook of Autism and Pervasive Developmental Disorders. Autism and Child Psychopathology Series. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-8065-6_30
28. Sabey, C., Ross, S., & Goodman, J. (2020, January 15). Beyond topography: addressing the functional impact of social skills training for students with autism. Educational Psychology in Practice, 36(2), 133–148. https://doi.org/10.1080/02667363.2019.1703650
29. Sanahuja, Josep & Tan, Qinyi. (2012). Improving the Process of Inclusive Education in Children with ASD in Mainstream Schools. Procedia - Social and Behavioral Sciences. 46. 4072-4076. 10.1016/j.sbspro.2012.06.200.
30. Sansi, A., Nalbant, S., & Ozer, D. (2020, September 17). Effects of an Inclusive Physical Activity Program on the Motor Skills, Social Skills and Attitudes of Students with and without Autism Spectrum Disorder. Journal of Autism and Developmental Disorders, 51(7), 2254–2270. https://doi.org/10.1007/s10803-020-04693-z
31. Schmidt, C., & Stichter, J. P. (2012, April 17). The Use of Peer-Mediated Interventions to Promote the Generalization of Social Competence for Adolescents with High-Functioning Autism and Asperger's Syndrome. Exceptionality, 20(2), 94–113. https://doi.org/10.1080/09362835.2012.669303
32. Scott, K. (2019, January 1). Teaching the Hidden Curriculum of Group Work for Students with Autism Spectrum Disorder. De Gruyter. https://doi.org/10.1515/edu-2019-0008
33. Sreckovic, M. A., Hume, K., & Able, H. (2017, May 31). Examining the Efficacy of Peer Network Interventions on the Social Interactions of High School Students with Autism Spectrum Disorder. Journal of Autism and Developmental Disorders, 47(8), 2556–2574. https://doi.org/10.1007/s10803-017-3171-8
34. Dat Tran, V. (2013). Theoretical perspectives underlying the application of cooperative learning in classrooms. International Journal of Higher Education, 2(4). 10.5430/ijhe.v2n4p101
35. Trottier, N., Kamp, L., & Mirenda, P. (2011, February 2). Effects of Peer-Mediated Instruction to Teach Use of Speech-Generating Devices to Students with Autism in Social Game Routines. Augmentative and Alternative Communication, 27(1), 26–39. https://doi.org/10.3109/07434618.2010.546810
36. Vincent, L. B., Asmus, J. M., Lyons, G. L., Born, T., Leamon, M., DenBleyker, E., & McIntire, H. (2022, April 20). Evaluating the effectiveness of a reverse inclusion Social Skills intervention for children on the Autism Spectrum. Journal of Autism and Developmental Disorders. https://doi.org/10.1007/s10803-022-05513-2
37. Zhang, B., Liang, S., Chen, J., Chen, L., Chen, W., Tu, S., Hu, L., Jin, H., & Chu, L. (2022, May). Effectiveness of peer-mediated intervention on social skills for children with autism spectrum disorder: a randomized controlled trial. Translational Pediatrics, 11(5), 663–675. https://doi.org/10.21037/tp-22-110

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Reliability and Validity Evaluation of the ''CLOX: An Executive Clock Drawing Task'' in a Greek Population with Neurological and Autoimmune Diseases

By Eleni Sideri, Ioanna Tsantzali, Claire Kelly, George Papadimitropoulos, Dimitrios Kitsos, Stella Fanouraki, Angeliki Sterpi, Georgios Tsivgoulis, George P. Paraskevas & Konstantinos I. Voumvourakis

National and Kapodistrian University of Athens

Abstract- Early and accurate detection of cognitive decline is a crucial factor for diagnosis, early interventions, and treatment strategies. The CLOX: an executive clock drawing task has emerged as a useful and frequent method for assessing cognitive abilities, especially in executive functioning domains. However, there are few normative data available for this tool. This protocol translates and validates the CLOX: an executive drawing task in the Greek population, also it tries to examine the use of CLOX in the Greek population. The study included a total number of participants 283 (76 males- 207 females) with mean ages 52,7 years, and a range of 19 to 90 years; the cohort consists of individuals with Dementia, Multiple Sclerosis, Systemic Lupus Erythematosus, and Mild Cognitive Impairment; The Internal consistency with a Cronbach's alpha value was .798 for CLOX task 1, .785 for CLOX task 2, and .874 for the overall scale (combining both tasks).

Keywords: CLOX; dementia; multiple sclerosis; systemic erythematosus lupus; mild cognitive impairment; validation.

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Abstract- Early and accurate detection of cognitive decline is a crucial factor for diagnosis, early interventions, and treatment strategies. The CLOX: an executive clock drawing task has emerged as a useful and frequent method for assessing cognitive abilities, especially in executive functioning domains. However, there are few normative data available for this tool. This protocol translates and validates the CLOX: an executive drawing task in the Greek population, also it tries to examine the use of CLOX in the Greek population. The study included a total number of participants 283 (76 males- 207 females) with mean ages 52,7 years, and a range of 19 to 90 years; the cohort consists of individuals with Dementia, Multiple Sclerosis, Systemic Lupus Erythematosus, and Mild Cognitive Impairment; The Internal consistency with a Cronbach's alpha value was .798 for CLOX task 1, .785 for CLOX task 2, and .874 for the overall scale (combining both tasks). These values indicate that the items in the CLOX tasks are measuring a coherent construct consistently. A one-way ANOVA analysis was performed to assess the effect of different disease types on CLOX task 1 and CLOX task 2 performance. The analysis revealed significant differences between disease groups for both tasks, while the Dementia group had the lowest mean scores.

Keywords: CLOX; dementia; multiple sclerosis; systemic erythematosus lupus; mild cognitive impairment; validation.

Author α σ ρ ¥ § χ ν: 2nd Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, "Attikon" General University Hospital, 12462 Athens, Greece.
e-mails: lenisideri1985@gmail.com, docjo1989@gmail.com, ge.papadim@gmail.com, dkitsos@icloud.com, stelfanou@gmail.com, angste1955@gmail.com, tsivgoulisgiorg@yahoo.gr
Author α ρ: Cardiff Metropolitan University, Applied Psychology Department Llandaff Campus, Western Avenue, Cardiff, CF5 2YB, Cardiff, Wales. e-mail: ckelly@cardiffmet.ac.uk
Corresponding Authors Θ ζ: 2nd Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, "Attikon" General University Hospital, 12462 Athens, Greece.
e-mails: cvoumvou@outlook.com, geoprskvs44@gmail.com

I. Introduction

Mr. X, a 78 y.o. retired Caucasian male accountant, breezed through the opening questions of his cognitive evaluation, confident that his sons were worrying needlessly about some lapses in his daily function that they had noticed. He smiled knowingly at the request of the neurologist to draw a clock face with all its markings and showing a specific time in its 12-hour span, having heard all about this test from friends and relatives. There was no reason to worry, couldn't he readily tell the time using his wristwatch, after all? It was only after he realized that there was something wrong with the lopsided ellipse with the missing numbers he kept drawing, that he realized there might be more to his children's worries. Scenes like this one are encountered with increasing frequency in aging populations. However, cognitive dysfunction can impact individuals of various age groups and isn't solely limited to the elderly population. Cognitive dysfunction can impact individuals of various age groups, not solely limited to the elderly population. This estimate is derived from the outcomes of specialized examinations and has been substantiated through prevalence studies, which have demonstrated cognitive impairments such as memory loss and executive dysfunction (Murman, 2015; Allott et al., 2016; Rosselli & Torres, 2019). Executive dysfunction involves deficits in cognitive processes such as attention, planning, decision-making, and problem-solving (Diamond, 2013), and is a common symptom seen in various neurological diseases (Amanzio et al., 2020). The frequency and severity of executive dysfunction can vary depending on the specific disease (Hanna-Pladdy, 2007). Incorporating cognitive assessments and screening tools into routine clinical practice is essential for the early detection and management of these conditions. By including cognitive assessments as part of the regular evaluation, healthcare professionals can identify cognitive impairments at an earlier stage, allowing for timely interventions and appropriate

management strategies (Vanderploeg, 2014). For instance, neuropsychological assessment plays a crucial role in clinical practice, particularly for conditions like dementia (Prado et al., 2019). These assessments have the potential to enhance the precision of diagnosis and facilitate the continual observation of illness progress. However, it is often noticed in clinical practise, specifically in the field of autoimmune illnesses, that there is a tendency to give higher priority to somatic symptoms, sensorimotor difficulties, and laboratory test results, while unintentionally overlooking cognitive deficits. By acknowledging the significance of cognitive assessments and integrating them into regular clinical practice, healthcare professionals can augment the thorough evaluation of patients, which results in enhanced early detection, suitable treatment, and improved overall patient well-being, that involve mental health.

Diseases like Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE) can be associated with cognitive decline. A significant percentage of patients with these conditions around 40-60% may experience impairments in cognitive functions such as memory, attention, and processing speed (Macías Islas & Ciampi, 2019; Mendelsohn et al., 2021). Regarding dementia, it is more commonly associated with older age and memory loss. The risk of developing dementia does increase with age, with most cases being diagnosed in individuals over the age of 65 (Brayne & Miller, 2017). However, it's important to note that some forms of dementia, such as early-onset Alzheimer's disease, can affect individuals as young as their 40s (Masellis et al., 2013). Besides this, there is often a challenge in distinguishing between mild cognitive impairment (MCI) and the spectrum of dementia (Knopman & Petersen, 2014). MCI refers to a stage where cognitive changes are present but do not meet the criteria for a diagnosis of dementia (Vega & Newhouse, 2014). There is no clear-cut between MCI and dementia, and it requires a comprehensive evaluation to make an accurate diagnosis (Lu et al., 2022). The discussed diseases have significant and complex molecular pathways and processes that differ and yet are similar to their clinical expression. On the other hand, neuroinflammation is the first negative observed effect in MS, then the results are myelin loss and axonal injury, whereas SLE leads to inflammation and affects the brain processes, both contributing to neurodegeneration (Mandel et al., 2004). Dementia, including Alzheimer's disease, is characterized by the presence of amyloid-beta plaques and tau protein tangles. However, the pathophysiology of SLE and MS is uncommonly associated with these molecules (Stancu et al., 2019). Additionally, small vessel disease and the reduced cerebral blood flow are significant contributors to MCI, Dementia with vascular involvement (Cai et al., 2015). These factors have as conswquence the vascular changes, which are not a requisite feature of systemic lupus erythematosus (SLE) or multiple sclerosis (MS), however, in many cases, the symptoms are presented respectively, but it depends on many factors for the appearance of vascular changes on MS and SLE (Jácome Sánchez et al., 2018). Therefore, the pathophysiological along with cognitive examination can help to recognize such brain dysfunctions, targeting each type to the situation and the brain region. This type of examination can interpret issues related to cognitive processes and functions of the brain, such as attention, memory, and problem-solving, to identify any abnormalities or disruptions that may be indicative of neurological or autoimmune conditions.

II. CLOX: An Executive Clock-drawing Task- the Tool Description

The CLOX drawing assessment meets all the criteria of a remarkable neuropsychological tool, as it enables the researchers, to quickly and easily, control a wide range of cognitive functions, including comprehension, design, visual memory, spatial abilities, motor organization, and executive function, involving individuals' knowledge, abstract thinking, inhibition of attraction to sensory stimuli, concentration, and tolerance to frustration (Royall et al., 1998). The CLOX's structure is divided into two parts, The purpose of dividing the CLOX task into two sections is to differentiate between the executive control aspects of drawing a clock and the basic ability to draw a clock. Typically, the first portion of the CLOX task requires individuals to draw a clock face from memory while following specific time-setting instructions. This section evaluates the ability to draw a timepiece and visuospatial skills. The second section of the CLOX exercise focuses on the executive control aspects of drawing a clock. It entails supplying individuals with specific instructions and requirements, such as setting the time to a specific hour or adding particular elements to the clock face. This section evaluates the candidate's ability to follow directions, plan, organize, and carry out tasks in a goal-directed manner. By dividing the task into two parts, researchers and clinicians can distinguish between individuals with deficits in fundamental clock-drawing skills and those with deficits in executive functions related to clock drawing. This separation can provide valuable insights into the cognitive processes involved in clock drawing and assist in identifying specific areas of difficulty in individuals with cognitive impairments or neurological disorders. this helps to be better recognized the performance between the executive control of the clock drawing and the clock drawing itself. Moreover, the first part (CLOX1) assesses executive functioning, and the second part (CLOX2) the visuospatial and visuoconstructive capacities (Royall et al., 1998). The individual takes instructions to draw a

clock that says 1:45 with the thought it is easy even a child could read this clock. This process is conducted on the empty page of the CLOX form, with no further instructions. The researcher repeats the instructions until they are totally understood, when the individual starts drawing no further details or aid can be given by the researcher. The researcher observes all the drawing procedures to score the 'CLOX1' (there is full detail for the scoring on the front page of the form). Then, follows the drawing procedures of 'CLOX2'. Initially, the researcher must perform the clock drawing while the individual observes the detailed process of drawing e.g. placing the 12, 6, 3, and 9 first. Then, the individual has to draw the CLOX2, and the researcher scores it accordingly (Royall et al., 1998) (please see Appendix 3)

A. Dementia and Clox Tasks

CLOX task has been extensively examined and used as an evaluative tool for cognitive dysfunction, particularly in the context of dementia, including Alzheimer's dis-ease (AD) (Kim et al., 2018; Rakusa et al., 2018). Royall et al., (1998; 1999) as the creators of CLOX: an executive clock drawing task, conducted many studies. One study examined the application of the CLOX task as a means of discriminating between persons afflicted with Alzheimer's disease and those affected by alternative types of dementia. The study's findings indicate that certain errors made during the CLOX task drawing exercise can effectively differentiate between Alzheimer's disease and non-Alzheimer's dementia, underscoring its diagnostic efficacy (Royall et al., 1999). Many studies have examined the longitudinal variations in the clox drawing tests performance of Alzheimer's disease patients (Lee et al., 2011). Deteriorating performance on the CLOX2 over time was associated with a progressive decline in cognitive function and the progression of Alzheimer's disease, according to the neuroimages and neuroanatomical findings (Shon et al., 2013). Similarly, it has been examined the performance of individuals with mild cognitive impairment (MCI), Alzheimer's disease, and healthy controls on the CLOX task, revealed an additional significant finding. They discovered that the CLOX2 component was particularly sensitive in distinguishing between MCI and Alzheimer's disease, indicating its diagnostic potential. These studies demonstrate the usefulness of the CLOX task for assessing executive functioning and cognitive impairment in patients with dementia spectrum disorders. They emphasize its diagnostic utility, longitudinal tracking abilities, and potential to distinguish between various forms of dementia (Huang et al., 2021). It is essential to note, that the specific results and implications of these studies may vary, and additional research is needed to continue the investigation of the CLOX task in dementia assessment. The multidimensional findings of brain mechanisms related to dementia and factors like biomarkers and brain segmentation are still under investigation.

B. Mild Cognitive Impairment and Clox Tasks

The CLOX task has been identified as a useful tool for distinguishing between individuals with Mild Cognitive Impairment (MCI) and those experiencing normal cognitive aging. Research has indicated that individuals diagnosed with mild cognitive impairment (MCI) exhibit inferior performance on the CLOX task in comparison to individuals without cognitive impairment, which suggests the presence of initial executive dysfunction (Kim et al., 2018; Rakusa et al., 2018). The CLOX task has shown promising results as a predictor of progression from mild cognitive impairment (MCI) to dementia (Kim et al., 2018). An adequate number of researches conducted over an extended period of time have demonstrated the correlation between suboptimal results on the CLOX task and a heightened susceptibility to the onset of dementia, including AD, among individuals diagnosed with mild cognitive impairment and cognitive complaints (Forti et al., 2010; McGuinness et al., 2015). The CLOX task has been determined to possess sensitivity in identifying cognitive alterations over a period in persons diagnosed with MCI. The deterioration of performance on the CLOX task may serve as an indicator of additional cognitive decline and advancement toward the onset of dementia (Forti et al., 2010). The integration of this test *with other cognitive assessments can yield a more helpful appraisal of cognitive dysfunction. Prof. Royall and his colleagues conducted research using the CLOX task to distinguish between individuals with MCI and healthy controls, as discussed previously. Although the findings were solid Royall et al. (2000) continued the research on this topic by employing neuropsychological batteries containing both cognitive and functional status measures in order to diagnose dementia more accurately relative to expert clinicians. Indicating that the use of Clox tasks in conjunction with tools such as the MMSE and IADL can enhance diagnostic performance and increase the likelihood of identifying MCI and dementia accurately (Royall et al., 2015). Similarly, Babins et.al., (2008) investigated the predictive value of the CLOX task for the progression of mild cognitive impairment to dementia. During follow-up evaluations, individuals with MCI who performed inadequately on the CLOX task at baseline were more likely to progress to dementia, including Alzheimer's disease.*

C. Multiple Sclerosis and Clox tasks

The relevance of the CLOX task in assessing executive functioning in individuals with Multiple Sclerosis has not been extensively examined, while many studies have used plenty of neuro psychometric tools (Rogers & Panegyres, 2007). For instance, Benedict et al. (2006) have used the Minimal Assessment of Cognitive Function in Multiple Sclerosis

(MACFIMS), which incorporates the CDT as one of its measures, this study investigated cognitive impairment in MS patients. According to their performance on the CDT, the authors discovered planning and organization deficits in MS patients. These findings have been suggested from similar studies, indicating that cognitive impairment in people with MS can be linked with poor performance on the CDT and general cognitive dysfunction (Achiron, 2003). Zwecker et al. (2018) used the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), clock-drawing test (CDT), and P300 Event-Related Potentials (ERPs) to assess cognitive impairments in MS patients. The key study findings were that 61.5% of 56 early-stage MS patients (less than 3 years) had sub-normal scores on at least two BRB-N or CDT cognition subtests; verbal fluency (88.6%), short-term memory (70.5%), visual-spatial learning (59.1%), CDT (45.5%), and sustained attention (29.5%) were impaired. However, a significant barrier to conducting CLOX tasks has been revealed by studies that have shown patients with MS often exhibit difficulties in performing the CDT due to motor disabilities. These difficulties may manifest as impaired planning and organization, reduced attention to detail, and difficulty conceptualizing and executing the task accurately. These deficits in CDT performance can be interpretative as cognitive impairment and can be used as an indicator of disease-related cognitive dysfunction in MS however, these occur because of spinal cord lesions related to MS (Lynch et al., 2005).

D. Systemic Lupus Erythematosus and Clox Tasks

There is a lack of studies to determine whether Clox tasks are effective in identifying cognitive impairment caused by systemic lupus erythematosus (SLE). Assessing cognitive impairment in SLE can be intricate due to factors such as the diversity of cognitive deficits, the influence of coexisting medical conditions, and the similarity with other neuropsychiatric symptoms of SLE (Seet et al., 2021). Neuropsychological assessments are commonly utilized to evaluate cognitive impairment in SLE, involving a battery of tests that focus on various cognitive domains (Nowicka-Sauer et al., 2011). However, the utilization of CLOX in SLE appears to be restricted. The validity and utility of the CLOX task in this context lack substantial evidence in the research literature in the knowledge of the authors. While neuropsychological tests that evaluate executive functioning in SLE are the Trail Making Test A and B, Stroop Test, and Wisconsin Card Sorting Test (Hanly et al., 2010). Nonetheless, it is pertinent to highlight some noteworthy research studies. Hanly et.al., (2006;2009;2010) have conducted many studies to examine cognitive impairment in individuals with SLE by utilizing a comprehensive neuropsychological battery to represent the initial exploration of cognitive-related SLE issues. Although the CLOX task was not explicitly referenced, researchers applied alternative cognitive evaluation measurements that focused on executive functions. According to Kozora et al. (2022) a significant proportion of individuals diagnosed with SLE demonstrate executive dysfunction, which has a discernible impact on their daily functioning. The researchers employed an innovative methodology to examine attentional and executive function in individuals with Systemic Lupus Erythematosus (SLE) using a digital platform. The findings of this study indicate that individuals diagnosed with SLE demonstrated significant improvements in their motor speed and executive functions. Hence, it has been highlighted that individuals diagnosed with SLE may present advantageous outcomes by engaging in cognitive interventions that are custom-designed to address the frontoparietal networks of the brain. It is crucial to note that the studies may involve a broader scope of assessments related to cognitive impairment and executive functioning in SLE, rather than solely concentrating on the CLOX task. However, additional research is required to address the limited amount of existing research on the utilization of the CLOX task in SLE. For this reason, a new research protocol would contribute to a more comprehensive comprehension of the cognitive difficulties experienced by individuals with SLE and facilitate the formulation of focused interventions and treatment strategies. Furthermore, it would be beneficial for future research to investigate alternative cognitive assessment tools that have the potential to capture various dimensions of cognitive functioning within the population affected by SLE. Additionally, given the numerous similarities with other autoimmune disorders like MS, it would be advantageous for researchers to employ specialized neuropsychological tools such as CLOX tasks. This approach would yield more accurate estimations of the results and facilitate meaningful comparisons and contrasts between these findings.

E. Aim of this Study

The purpose of this study is to validate the neuropsychological tool -CLOX: An Executive Clock-Drawing Task- to the Greek population and recognize its reliability in disease existence. Based on previous studies, the CLOX: an executive clock drawing task has been proven a useful neuropsychological tool for the assessment of executive function impairment. However, to the best of the researchers' knowledge, no previous protocol has aimed to validate the screening qualities of CLOX: an executive clock drawing and scoring system on the Greek population. Moreover, there has been no prior endeavor to validate the psychometric properties of this instrument on the Greek population diagnosed with Multiple Sclerosis, Systemic Erythematosus Lupus, Dementia spectrum, and MCI.

III. Methodology

1. Participants

The study included a total number of participants 283 (76 males/207 females) who had visited the 2nd Neurology Department of Attikon University in the last 18 months, they were examined by experienced neurologists and psychologists who recorded data such as demographics and disease history. It is a convenient sample. The mean age of the subjects was 52,7 years, with a range 19-90; the mean number of years of education was 13 years with a range of 3-21 years. The subjects were divided based on their diagnosis and health control, therefore, patients with MCI (n = 44; 15.5 % of the total sample), patients with Dementia types (n = 58: Dementia=39, AD =19, 20.1%), patients with MS (n = 68; 24.0% of the total sample), patients with SLE (n = 71, 25.1% of the total sample), and the healthy controls (n = 43; 15.2% of the total sample) (please, see Table 1). The recruitment of participants diagnosed with Dementia spectrum and Mild Cognitive Impairment (MCI) were enrolled based on their magnetic resonance imaging (MRI) findings and other relevant clinical assessments conducted prior to their inclusion in the study. The examinations encompass the analysis of specific molecules, namely phosphorylated tau (p-tau) and amyloid-beta (Aβ), which have been extensively researched in relation to mild cognitive impairment (MCI) and Alzheimer's disease (AD). Also, biomarkers, such as cerebrospinal fluid (CSF) levels of p-tau and Aβ, along with neuroimaging measures like frontotemporal type (FT-MCI), frontotemporal dementia (FTD), and normal pressure hydrocephalus (NPH), are being investigated as potential diagnostic and prognostic markers for mild cognitive impairment (MCI) and its progression to dementia. Inclusion criteria were diagnosis of the following diseases: dementia and Alzheimer's Disease based on DSM-V, with a previous clinical examination with cerebrospinal fluid (CSF) biomarker measurements such as beta-amyloid 42, tau, and phospho-tau as they are considered a hallmark for the diagnosis (Ashton et al., 2022), and structural brain imaging (CT or MRI); the individuals with MS were recruited as they had a definite diagnosis of MS according to the McDonald criteria 2017 (McDonald Criteria, 2022), their clinical condition was stable without relapses the last 6 months, they had MRI and they had expressed cognitive issues also they had previous examinations with biomarkers such as IL-6, CD14 e.g ; individuals with SLE with a diagnosis that meet the revised American College of Rheumatology (ACR) classification criteria, they had an MRI and had expressed cognitive issues; Healthy controls were random health visitors of the clinic as well as university students. Additional inclusion criteria; All participants were aged over 18 years, able to speak and read Greek fluently, and provide themself or/and their caregivers with full detailed information and consent forms. Exclusion criteria were any type of comorbidities such as cardiovascular disease and psychiatric disorder; individuals with motor deficits in handwriting; other reasons such as medication or/and alcohol use that may affect participants' mental function and/or mental health; participants with a covid-19 diagnosis were excluded.

2. Ethics

The researchers requested permission from Professor Donald Royall, the creator of CLOX: Clock Drawing Executive Test. The researchers were granted permission, thereby facilitating the validation process to proceed. Following that, the investigators provided a thorough account of the research protocol, encompassing the methodologies for conducting the study and acquiring approval from the Attikon University Hospital Ethics Committee. The reference number assigned to the protocol in question is identified as 'BNEYR, EBD366/16-7-2021'. The researchers followed the guidelines specified in the General Data Protection Regulation (GDPR) throughout the entire study, thus guaranteeing the safeguarding of the participants' information.

3. Procedure

All stages of the protocol were conducted at Attikon University Hospital. The participants recruited in the 2nd Neurological Department were assessed using interviews and a neuropsychological examination. The chosen location was specifically designed to facilitate the administration of the psychometric test in a controlled environment, devoid of any extraneous stimuli, such as sound. The process began by informing the participants about their involvement. After obtaining their consent, the interview proceeded by gathering demographic information and relevant documentation, including MRIs and biomarker tests, to validate their condition. The participants subsequently underwent a series of neuropsychological tests. The recruitment process spans a period of 18 months. The researchers implemented comprehensive measures to ensure the well-being of the participants, specifically focusing on mitigating the risks associated with the COVID-19 pandemic. or the diagnosis (Ashton et al., 2022), and structural brain imaging (CT or MRI); the individuals with MS were recruited as they had a definite diagnosis of MS according to the McDonald criteria 2017 (McDonald Criteria, 2022), their clinical condition was stable without relapses the last 6 months, they had MRI and they had expressed cognitive issues also they had previous examinations with biomarkers such as IL-6, CD14 e.g; individuals with SLE with a diagnosis that meet the revised American College of Rheumatology (ACR) classification criteria, they had an MRI and had expressed cognitive issues; Healthy controls were random health visitors of the clinic as well as university

students. Additional inclusion criteria; All participants were aged over 18 years, able to speak and read Greek fluently, and provide themself or/and their caregivers with full detailed information and consent forms. Exclusion criteria were any type of comorbidities such as cardiovascular disease and psychiatric disorder; individuals with motor deficits in handwriting; other reasons such as medication or/and alcohol use that may affect participants' mental function and/or mental health; participants with a covid-19 diagnosis were excluded.

Table 1: Sample Frequencies

Disease Type	Frequency	Percentage
Mild Cognitive Impairment	44	15.5%
Dementia	57	20.1%
Multiple Sclerosis	68	24.0%
Systemic Lupus Erythematosus	71	25.1%
Health Control	43	15.2%

IV. Results

a) Internal consistency

The reliability of CLOX: an Executive Clock-Drawing Task, has been investigated as a scale of measurement in the Greek population. This examination focused on individuals with specific diseases, including MCI, dementia spectrum disorders, MS, SLE, and health control. A total of 283 participants successfully completed the scale. The evaluation of the internal consistency of the CLOX task was conducted based on the reported Cronbach's alpha values. The initial task, comprising 15 items, exhibited satisfactory internal consistency, as indicated by a Cronbach's alpha coefficient of .798. The second task, which also comprised 15 items, demonstrated satisfactory internal consistency, as evidenced by a Cronbach's alpha coefficient of .785. When examining the comprehensive scale comprising all 30 items, the internal consistency was found to be highly satisfactory, as indicated by a Cronbach's alpha coefficient of .874. The results of this study indicate that the CLOX: An Executive Clock-Drawing Task demonstrates a high level of reliability as a tool for evaluating executive functioning and cognitive impairment in the Greek population. This is particularly applicable to individuals with MCI, dementia, MS, and SLE. The high level of internal consistency, ranging from good to very good, suggests that the items within the CLOX task are effectively measuring a cohesive construct in a reliable manner. Therefore, the study proposes that the CLOX: An Executive Clock-Drawing Task is a dependable tool for evaluating executive functioning and cognitive impairment in the Greek population, particularly in individuals diagnosed with MCI, dementia, MS, and SLE, based on the obtained results. The high level of internal consistency observed in the task suggests that the items comprising the CLOX task consistently assess the targeted construct of executive functioning and cognitive impairment.

b) Construct Validity

A Principal Component Analysis (PCA) was conducted on the CLOX task 1 items. The interpretations of Kaiser-Meyer-Olkin Measure of Sampling Adequacy: .787 indicates that the sample used in the analysis is considered adequate for conducting PCA. Generally, a value above .6 is considered acceptable. Bartlett's Test of Sphericity ($\chi 2105 = 1097.418$ ($<.001$) suggests that the correlation matrix is not an identity matrix, indicating that there is a sufficient correlation among the variables for PCA to be meaningful. Therefore, the significant p-value of less than 0.001 suggests that there is enough correlation among the variables in the CLOX task 1 items, indicating that PCA is meaningful and can be applied to extract underlying factors or dimensions from the data. For example, for CLOX1.1, the initial commonality is 1.000, indicating that the item explains 100% of its own variance. The extraction communality is .428, suggesting that this item shares some common variance with the other items in the analysis (please see Appendix 1). Total Variance Explained shows the first component explains 27.360% of the variance, the second component explains 12.006%, and so on. The cumulative percentage indicates how much total variance is explained by the successive components. For example, the first two components explain a cumulative percentage of 39.366%. Therefore, the PCA results suggest that there are several components (factors) that contribute to the variation in the CLOX task 1 items. The first few components explain a significant proportion of the variance, while the subsequent components contribute less.

In the same spirit, the Kaiser-Meyer-Olkin Measure of Sampling Adequacy for CLOX task 2 is .733,

suggesting that the data used for factor analysis is reasonably adequate. Bartlett's Test of Sphericity examines the correlation matrix presenting (χ2105 =1436.865, p< 0.001). This result suggests that the correlation matrix is significantly different from an identity matrix, indicating that the variables are likely correlated and suitable for factor analysis. The extraction communalities range from 0.363 to 0.894, indicating the amount of variance explained by the factors after extraction. The first component explains 27.533% of the variance, and cumulatively, the first three components explain 50.877% of the variance. In the rotation sums of squared loadings, the first component explains 16.845% of the variance, and cumulatively, the first three components explain 46.042% of the variance (please see Appendix 2). Based on these results, it appears that there are meaningful components or factors in the data that explain a significant proportion of the variance.

c) The Effect of Disease Types on CLOX Performance

One-way ANOVAs were run with Disease Diagnosis as the IV and CLOX scores as the DV (Tukey's HSD was used for pairwise comparisons). There was a main effect of Disease Diagnosis on CLOX1 Scores (F4,272=37.599, p<.001) where pairwise comparisons showed that all Disease Diagnoses were associated with poorer performance than Healthy Controls (all at p<.001), and those with a Dementia diagnosis performed worse than those with any other Disease Diagnosis (all at p<.001 see Figure 1).

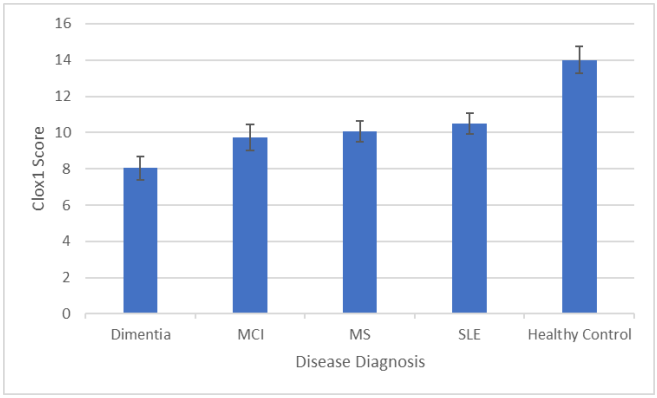

Figure 1: Mean CLOX1 Score by Disease Diagnosis (error bars show 95% CI).

There was also a main effect of Disease Diagnosis on CLOX2 scores (F4, 278=34.1, p<.001) where pairwise comparisons showed that all Disease Diagnoses were associated with poorer performance than Healthy Controls (all at p<.001) and those with a Dementia diagnosis performed worse than those with any other Disease Diagnosis (all at p<.001 see Figure 2).

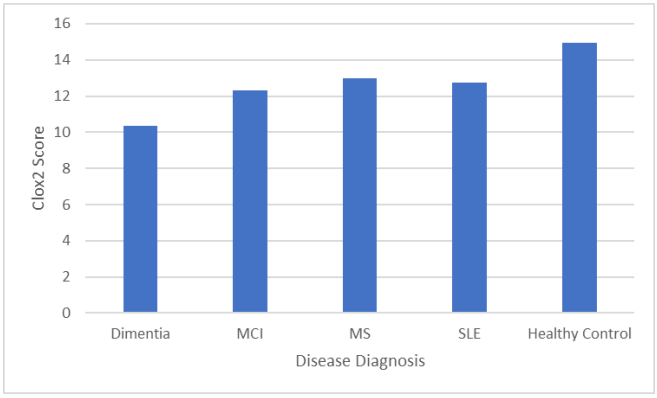

Figure 2: Mean CLOX2 Score by Disease Diagnosis (error bars show 95% CI).

The results of this analysis suggest that individuals with MCI, SLE, MS, and dementia diagnoses exhibit lower performance on both the CLOX1 and CLOX2 tasks in comparison to a control group consisting of healthy individuals. Moreover, when it comes to disease diagnoses, individuals diagnosed with Dementia exhibit notably poorer performance on both tasks in comparison to individuals diagnosed with other diseases. The findings of this study indicate that the scores of CLOX1 and CLOX2 have the potential to be valuable indicators for differentiating between Healthy Controls and individuals diagnosed with SLE, MS, MCI, and specifically Dementia.

ROC curves and CLOX task1 and Task2 In accordance with the above findings, have run a ROC curve analysis as it is a valuable tool in psychometric validation, providing insights into the discriminatory power, optimal cut-off point, comparative analysis, and diagnostic accuracy of the CLOX as a tool. The Area Under the ROC Curve (AUC) is a commonly employed performance metric for classifiers and diagnostic tests. It measures the test's ability to distinguish between positive and negative cases. In our case, the AUC values for the variables represent test results. The test result variables being evaluated based on the ROC curve analysis are CLOX task 1 total score and CLOX task 2 total score. The actual condition being evaluated is Health Control. The Area Under the ROC Curve for CLOX task 1 was 0.938 and for CLOX task 2, it was 0.940. The AUC values indicate that both scores have a high ability to differentiate between genuine positive and negative states. The Classifier Evaluation Metrics provide additional information regarding the efficacy of the classifiers based on the Gini Index and the Kolmogorov-Smirnov (K-S) statistics.

Classifier Performance Metrics:

CLOXtask1 total score: Gini Index: 0.876, Max K-S Statistics: 0.759, Cutoff: 12.0000;

CLOXtask2 total score: Gini Index: 0.880, Max K-S Statistics: 0.834, Cutoff: 14.0000;

Both CLOX task1 total score and CLOX task 2 total score demonstrate strong performance in differentiating between positive and negative actual states, with CLOX task 2 having a slightly higher Area Under the ROC Curve. The Gini Index quantifies the disparity in the distribution of predicted probabilities. A higher Gini Index indicates a more effective classifier. In our case, the Gini Index for CLOX1.The total is 0.876, whereas it is 0.880 for CLOX2.Total. These values indicate that both classifiers have a high capacity for discrimination in predicting the actual positive state of Health Control. The K-S Statistics measure the greatest disparity between the cumulative distribution functions of the positive and negative categories. It indicates the classifier's capacity to distinguish between the two groups. CLOX task 1 total score and CLOX task 2 total score have Max K-S values of 0.75 and 0.83, respectively. The greater the Max K-S value, the more efficient the classifier. In both instances, the Max K-S values reported are associated with particular cut-off values. If multiple cut-off values exist, the largest is reported. These Max K-S values indicate that both the scores classifiers are able to distinguish between positive and negative actual states (please see the Figure 3 and 4).

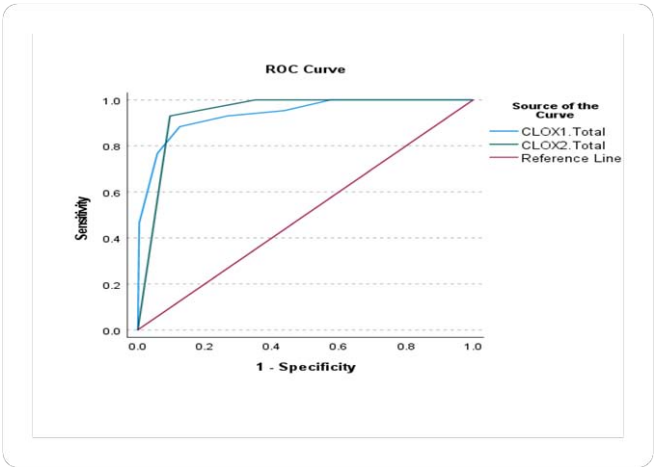

Figure 3: ROC curve

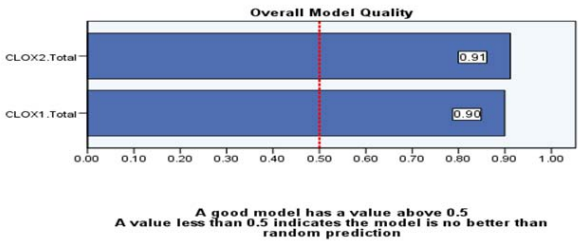

Figure 4: Model Quality

V. Conclusion

The present study aimed to investigate the effectiveness of the CLOX: an Executive Clock-Drawing Task assessment in the Greek population. The availability of valid and reliable data is crucial in establishing representative performance for cultural elements as well as the disease of interest. Understanding the effectiveness of this assessment can have important implications for clinical and research settings. This investigation included a sample of the Greek population with varying types of diseases. The researchers aimed to make the sample as representative as possible of most age ranges. The study recruited participants from multiple clinical settings and ensured that individuals with MCI, dementia, MS, and SLE were included. The internal consistency and construct validity of the CLOX assessment provide strong evidence for its reliability and validity. This suggests that the CLOX assessment can be a valuable tool in clinical settings for diagnosing and monitoring individuals with MCI, dementia, MS, and SLE. However, it is important to note that our study had certain limitations. One limitation of our study is that we relied on specific neuropsychological tools, which may introduce potential bias, a more comprehensive approach to neuropsychological tests could have provided a more holistic understanding of cognitive functioning and psychosocial impact. Future studies could consider incorporating a wider range of assessments to capture the complexity of these disorders. Additionally, it used a relatively small sample size. These limitations should be considered when interpreting the results. Prior research, however, has explored the disease of MS, SLE, dementia, and MCI from a more holistic neuropsychological perspective, revealing the complex consequences of these disorders on cognitive functioning, emotional well-being, quality of life, and functional skills. Studies on MS, for example, have looked at comprehensive neuropsychological assessments that include cognitive testing, emotional assessment, and functional evaluation to capture the disease's cognitive and psychosocial impact (Benedict et al., 2017; Goverover et al., 2016). These studies frequently look at the connections between cognitive deficits, mood disorders, fatigue, and quality of life measurements in people with MS. Regarding SLE, studies have mainly focused on cognitive functioning, psychological welfare, and disease-related factors. Comprehensive neuropsychological batteries, as well as measures of depression, anxiety, disease activity, and quality of life, may be used in these investigations (Hanly et al., 2009; 2010). However, the goal is to comprehend the cognitive and psychosocial consequences of SLE as a primary factor in the disease onset, and also to understand link factors to the disease progress. In the case of dementia and MCI, holistic methods of neuropsychological examinations strive to capture cognitive functioning, functional abilities, mood abnormalities, and quality of life in these patients. Comprehensive assessment batteries, which include measures of cognition, functional abilities, psychiatric symptoms, and well-being, have been studied to provide a holistic understanding of an individual's cognitive decline and its impact on daily functioning (Hussenoeder et al., 2020). In the same way, there have been numerous research conducted to investigate the sex differentiations in cognitive abilities. It is crucial to acknowledge that although there are certain overarching patterns, there are significant individual variations within each sex category, and any detected disparities should not be taken as indicative of an individual's skills. Unfortunately, a notable variation in participant numbers between males and females is evident in this study. The past decade has seen a significant increase in studies on sex differences in executive function, particularly those using functional neuroimaging. Despite this growing body of knowledge, the effects of sex on executive function are still poorly understood due to methodological variability in executive function task selection, participant inclusion and exclusion criteria, and scanning procedures (Gaillard, Fehring & Rossell, 2021). A significant review suggested that the executive functions of monitoring, response inhibition, and cognitive shifting as executive function domains present differentiations, however, there is a need for further investigation. It is imperative to acknowledge this constraint to account for the impact of health, societal, and cultural influences on sex variations in cognitive test performance, especially in the discussed diseases. This study encompassed individuals ranging in age from 18 to 90 years old. The researchers tried to get a representative sample that covered each phase of human life. The aim of validating this specific psychometric tool is to enable its application in individuals diagnosed with neuroinflammatory and neurodegenerative diseases, or those suspected to have a decline in executive function. The purpose is to assess the individual's abilities in executive functioning by evaluating their approach to what was given to them. The participants are examined on variables that indicate the presence of adverse signs of planning, organization, initiation, and cognitive flexibility. Consequently, a well-executed clock drawing may suggest intact executive functioning, while errors or omissions may indicate executive dysfunction. Furthermore, the inclusion of participants from different age groups, including both younger and older individuals, enables researchers to discern patterns of cognitive performance across various stages of development. Also, including younger and older participants allows researchers to identify developmental trends in cognitive performance. For example, they can observe how executive functioning skills develop in young adults and whether they decline

or remain stable in older adults. Moreover, can be a helpful tool for the researchers to explore why some older individuals maintain strong executive functioning skills while others experience declines, potentially uncovering protective factors or interventions that promote cognitive health.

Conclusions

To conclude CLOX: An Executive Clock-Drawing is a reliable and valid tool in the Greek population with the disorders described above suggesting that the CLOX assessment shows promise as a valuable tool for assessing executive function in individuals with specific disorders. Despite the positive findings in the Greek population with the described disorders, it is important to validate the reliability and validity of the CLOX assessment in other populations and with a broader range of disorders. This will help establish the generalizability of the findings and determine if the CLOX assessment can be used as a reliable tool across different clinical and research contexts. This ongoing research will enhance our understanding of the value and applicability of the CLOX assessment.

Supplementary Materials: Not applicable

Author Contributions: Conceptualization Eleni Sideri; George P.Paraskevas; investigation, Eleni Sideri; Ioanna Tsantzali; resources, Georgios N. Papadimitropoulos, Claire Kelly, Dimitrios Kitsos, Stella Fanouraki, Angeliki Sterpi; writing—original draft preparation, Eleni Sideri; Ioanna Tsantzali; formal analysis, Eleni Sideri; George P.Paraskevas; George Tsivgoulis writing—review and editing, George Papadimitropoulos, Eleni Sideri, Claire Kelly; supervision, George P.Paraskevas, and Konstantinos Voumvourakis. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study, also, there is written informed consent has been obtained from the participants to publish any paper related to this data.

Data Availability Statement: Due to restrictions of the ethics committee patients' data cannot become publicly available, however, they may be provided by the correspondent author according to a reasonable request

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Conflicts of Interest: Not applicable.

References Références Referencias

1. Achiron, A. (2003). Cognitive impairment in probable multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(4), 443–446. https://doi.org/10.1136/jnnp.74.4.443
2. Allott, K., Fisher, C. A., Amminger, G. P., Goodall, J., & Hetrick, S. (2016). Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain and Behavior*, *6*(10), e00527. https://doi.org/10.1002/brb3.527
3. Amanzio, M., Bartoli, M., Cipriani, G. E., & Palermo, S. (2020). Executive Dysfunction and Reduced Self-Awareness in Patients With Neurological Disorders. A Mini-Review. *Frontiers in Psychology*, *11*. https://doi.org/10.3389/fpsyg.2020.01697
4. Ashton, N. J., Benedet, A. L., Pascoal, T. A., Karikari, T. K., Lantero-Rodriguez, J., Brum, W. S., Mathotaarachchi, S., Therriault, J., Savard, M., Chamoun, M., Stoops, E., Francois, C., Vanmechelen, E., Gauthier, S., Zimmer, E. R., Zetterberg, H., Blennow, K., & Rosa-Neto, P. (2022). Cerebrospinal fluid p-tau231 as an early indicator of emerging pathology in Alzheimer's disease. *EBioMedicine*, *76*. https://doi.org/10.1016/j.ebiom.2022.103836
5. Babins, L., Slater, M.-E., Whitehead, V., & Chertkow, H. (2008). Can an 18-point clock-drawing scoring system predict dementia in elderly individuals with mild cognitive impairment? *Journal of Clinical and Experimental Neuropsychology*, *30*(2), 173–186. https://doi.org/10.1080/13803390701336411
6. Bendict, R. H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12*(04). https://doi.org/10.1017/s1355617706060723
7. Benedict, R. H. B., DeLuca, J., Enzinger, C., Geurts, J. J. G., Krupp, L. B., & Rao, S. M. (2017). Neuropsychology of Multiple Sclerosis: Looking Back and Moving Forward. *Journal of the International Neuropsychological Society*, *23*(9-10), 832–842. https://doi.org/10.1017/s1355617717000959
8. Brayne, C., & Miller, B. (2017). Dementia and aging populations—A global priority for contextualized research and health policy. *PLOS Medicine*, *14*(3), e1002275. https://doi.org/10.1371/journal.pmed.1002275
9. Cai, Z., Wang, C., He, W., Tu, H., Tang, Z., Xiao, M., & Yan, Liang-Jun. (2015). Cerebral small vessel disease and Alzheimer's disease. *Clinical Interventions in Aging*, *10: 1695–704*(10:1695–704), 1695. https://doi.org/10.2147/cia.s90871

10. Diamond, A. (2013). Executive Functions. *Annual Review of Psychology*, *64*(1), 135–168. https://doi.org/10.1146/annurev-psych-113011-143750
11. Forti, P., Olivelli, V., Rietti, E., Maltoni, B., & Ravaglia, G. (2010). Diagnostic Performance of an Executive Clock Drawing Task (CLOX) as a Screening Test for Mild Cognitive Impairment in Elderly Persons with Cognitive Complaints. *Dementia and Geriatric Cognitive Disorders*, *30*(1), 20–27. https://doi.org/10.1159/000315515
12. Gaillard, A., Fehring, D. J., & Rossell, S. L. (2021). Sex differences in executive control: A systematic review of functional neuroimaging studies. European Journal of Neuroscience, 53(8), 2592-2611.
13. Goverover, Y., Genova, H. M., DeLuca, J., & Chiaravalloti, N. D. (2016). Impact of Multiple Sclerosis on Daily Life. *Changes in the Brain*, 145–165. https://doi.org/10.1007/978-0-387-98188-8_7
14. Hanly, J. G., Omisade, A., Su, L., Farewell, V., & Fisk, J. D. (2010). Assessment of cognitive function in systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis by computerized neuropsychological tests. *Arthritis & Rheumatism*, *62*(5), 1478–1486. https://doi.org/10.1002/art.27404
15. Hanly, J. G., Su, L., Farewell, V., McCurdy, G., Fougere, L., & Thompson, K. (2009). Prospective Study of Neuropsychiatric Events in Systemic Lupus Erythematosus. *The Journal of Rheumatology*, *36*(7), 1449–1459. https://doi.org/10.3899/jrheum.081133
16. Hanly, J. G., Urowitz, M. B., Sanchez-Guerrero, J., Bae, S. C., Gordon, C., Wallace, D. J., Isenberg, D., Alarcón, G. S., Clarke, A., Bernatsky, S., Merrill, J. T., Petri, M., Dooley, M. A., Gladman, D., Fortin, P. R., Steinsson, K., Bruce, I., Manzi, S., Khamashta, M., & Zoma, A. (2006). Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: An international inception cohort study. *Arthritis & Rheumatism*, *56*(1), 265–273. https://doi.org/10.1002/art.22305
17. Hanna-Pladdy, B. (2007). Dysexecutive Syndromes in Neurologic Disease. *Journal of Neurologic Physical Therapy*, *31*(3), 119–127. https://doi.org/10.1097/npt.0b013e31814a63c2
18. Huang, Y., Pan, F.-F., Huang, L., & Guo, Q. (2021). The Value of Clock Drawing Process Assessment in Screening for Mild Cognitive Impairment and Alzheimer's Dementia. *Assessment*, *30*(2), 107319112110538. https://doi.org/10.1177/10731911211053851
19. Hussenoeder, F. S., Conrad, I., Roehr, S., Fuchs, A., Pentzek, M., Bickel, H., Moesch, E., Weyerer, S., Werle, J., Wiese, B., Mamone, S., Brettschneider, C., Heser, K., Kleineidam, L., Kaduszkiewicz, H., Eisele, M., Maier, W., Wagner, M., Scherer, M., & König, H.-H. (2020). Mild cognitive impairment and quality of life in the oldest old: a closer look. *Quality of Life Research*, *29*(6), 1675–1683. https://doi.org/10.1007/s11136-020-02425-5
20. Jácome Sánchez, E. C., García Castillo, M. A., González, V. P., Guillén López, F., & Correa Díaz, E. P. (2018). Coexistence of systemic lupus erythematosus and multiple sclerosis. A case report and literature review. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *4*(2), 205521731876833. https://doi.org/10.1177/2055217318768330
21. Kim, S., Jahng, S., Yu, K.-H., Lee, B.-C., & Kang, Y. (2018). Usefulness of the Clock Drawing Test as a Cognitive Screening Instrument for Mild Cognitive Impairment and Mild Dementia: an Evaluation Using Three Scoring Systems. *Dementia and Neurocognitive Disorders*, *17*(3), 100. https://doi.org/10.12779/dnd.2018.17.3.100
22. Knopman, D. S., & Petersen, R. C. (2014). Mild Cognitive Impairment and Mild Dementia: A Clinical Perspective. *Mayo Clinic Proceedings*, *89*(10), 1452–1459. https://doi.org/10.1016/j.mayocp.2014.06.019
23. Kozora, E., Zell, J. L., Baraghoshi, D., Smith, R. M., & Strand, M. (2022). Improved executive function in patients with systemic lupus erythematosus following interactive digital training. *Lupus*, *31*(8), 910–920. https://doi.org/10.1177/09612033221098534
24. Lee, J. H., Oh, E. S., Jeong, S. H., Sohn, E. H., Lee, T. Y., & Lee, A. Y. (2011). Longitudinal changes in clock drawing test (CDT) performance according to dementia subtypes and severity. *Archives of Gerontology and Geriatrics*, *53*(2), e179–e182. https://doi.org/10.1016/j.archger.2010.08.010
25. Lu, Y., Liu, G., Wells, Y., & Yu, D. (2022). Challenges in detecting and managing mild cognitive impairment in primary care: a focus group study in Shanghai, China. *BMJ Open*, *12*(9), e062240–e062240. https://doi.org/10.1136/bmjopen-2022-062240
26. Lynch, S. G., Parmenter, B. A., & Denney, D. R. (2005). The association between cognitive impairment and physical disability in multiple sclerosis. *Multiple Sclerosis Journal*, *11*(4), 469–476. https://doi.org/10.1191/1352458505ms1182oa
27. Macías Islas, M., & Ciampi, E. (2019). Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. *Biomedicines*, *7*(1), 22. https://doi.org/10.3390/biomedicines7010022
28. Mandel, M., Gurevich, M., Pauzner, R., Kaminski, N., & Achiron, A. (2004). Autoimmunity gene expression portrait: specific signature that intersects or differentiates between multiple sclerosis and systemic lupus erythematosus. *Clinical and Experimental Immunology*, *138*(1), 164–170. https://doi.org/10.1111/j.1365-2249.2004.02587.x

29. Masellis, M., Sherborn, K., Neto, P., Sadovnick, D. A., Hsiung, G.-Y. R., Black, S. E., Prasad, S., Williams, M., & Gauthier, S. (2013). Early-onset dementias: diagnostic and etiological considerations. *Alzheimer's Research & Therapy*, *5*(Suppl 1), S7. https://doi.org/10.1186/alzrt197
30. *McDonald criteria*. (2022, April 1). MS Trust. https://mstrust.org.uk/a-z/mcdonald-criteria
31. McGuinness, B., Barrett, S. L., McIlvenna, J., Passmore, A. P., & Shorter, G. W. (2015). Predicting conversion to dementia in a memory clinic: A standard clinical approach compared with an empirically defined clustering method (latent profile analysis) for mild cognitive impairment subtyping. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *1*(4), 447–454. https://doi.org/10.1016/j.dadm.2015.10.003
32. Mendelsohn, S., Khoja, L., Alfred, S., He, J., Anderson, M., DuBois, D., Touma, Z., & Engel, L. (2021). Cognitive impairment in systemic lupus erythematosus is negatively related to social role participation and quality of life: A systematic review. *Lupus*, 096120332110310. https://doi.org/10.1177/09612033211031008
33. Murman, D. (2015). The Impact of Age on Cognition. *Seminars in Hearing*, *36*(03), 111–121. https://doi.org/10.1055/s-0035-1555115
34. Nowicka-Sauer, K., Czuszynska, Z., Smolenska, Z., & Siebert, J. (2011). Neuropsychological assessment in systemic lupus erythematosus patients: clinical usefulness of first-choice diagnostic tests in detecting cognitive impairment and preliminary diagnosis of neuropsychiatric lupus. *Clinical and Experimental Rheumatology*, *29*(2), 299–306. https://pubmed.ncbi.nlm.nih.gov/21418780/
35. Prado, C. E., Watt, S., Treeby, M. S., & Crowe, S. F. (2019). Performance on neuropsychological assessment and progression to dementia: A meta-analysis. *Psychology and Aging*, *34*(7), 954–977. https://doi.org/10.1037/pag0000410
36. Rakusa, M., Jensterle, J., & Mlakar, J. (2018). Clock Drawing Test: A Simple Scoring System for the Accurate Screening of Cognitive Impairment in Patients with Mild Cognitive Impairment and Dementia. *Dementia and Geriatric Cognitive Disorders*, *45*(5-6), 326–334. https://doi.org/10.1159/000490381
37. Rogers, J. M., & Panegyres, P. K. (2007). Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations. *Journal of Clinical Neuroscience*, *14*(10), 919–927. https://doi.org/10.1016/j.jocn.2007.02.006
38. Rosselli, M., & Torres, V. L. (2019). Executive Dysfunction During Normal and Abnormal Aging. *Dysexecutive Syndromes*, 155–175. https://doi.org/10.1007/978-3-030-25077-5_8
39. Royall, D. R., Chiodo, L. K., & Polk, M. J. (2000). Correlates of Disability Among Elderly Retirees With "Subclinical" Cognitive Impairment. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *55*(9), M541–M546. https://doi.org/10.1093/gerona/55.9.m541
40. Royall, D. R., Cordes, J. A., & Polk, M. (1998). CLOX: an executive clock drawing task. *Journal of Neurology, Neurosurgery & Psychiatry*, *64*(5), 588–594. https://doi.org/10.1136/jnnp.64.5.588
41. Royall, D. R., Matsuoka, T., Palmer, R. F., Kato, Y., Taniguchi, S., Ogawa, M., Fujimoto, H., Okamura, A., Shibata, K., Nakamura, K., Shutaro Nakaaki, Hiroyuki Koumi, Mimura, M., Fukui, K., & Narumoto, J. (2015). Greater than the sum of its parts: δ Improves upon a battery's diagnostic performance. *Neuropsychology*, *29*(5), 683–692. https://doi.org/10.1037/neu0000153
42. Royall, D. R., Mulroy, A. R., Chiodo, L. K., & Polk, M. J. (1999). Clock Drawing Is Sensitive to Executive Control: A Comparison of Six Methods. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *54B*(5), P328–P333. https://doi.org/10.1093/geronb/54b.5.p328
43. Seet, D., Allameen, N. A., Tay, S. H., Cho, J., & Mak, A. (2021). Cognitive Dysfunction in Systemic Lupus Erythematosus: Immunopathology, Clinical Manifestations, Neuroimaging and Management. *Rheumatology and Therapy*, *8*(2), 651–679. https://doi.org/10.1007/s40744-021-00312-0
44. Shon, J. M., Lee, D. Y., Seo, E. H., Sohn, B. K., Kim, J. W., Park, S. Y., Kim, S. G., Jhoo, J. H., & Woo, J. I. (2013). Functional neuroanatomical correlates of the executive clock drawing task (CLOX) performance in Alzheimer's disease: A FDG-PET study. *Neuroscience*, *246*(23673275), 271–280. https://doi.org/10.1016/j.neuroscience.2013.05.008
45. Stancu, I.-C., Cremers, N., Vanrusselt, H., Couturier, J., Vanoosthuyse, A., Kessels, S., Lodder, C., Brône, B., Huaux, F., Octave, J.-N., Terwel, D., & Dewachter, I. (2019). Aggregated Tau activates NLRP3–ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. *Acta Neuropathologica*, *137*(4), 599–617. https://doi.org/10.1007/s00401-018-01957-y
46. Vanderploeg, R. D. (2014). Clinician's Guide To Neuropsychological Assessment. In *Google Books*. Psychology Press. https://books.google.at/books?id=rNZ4AgAAQBAJ
47. Vega, J. N., & Newhouse, P. A. (2014). Mild Cognitive Impairment: Diagnosis, Longitudinal Course, and Emerging Treatments. *Current Psychiatry Reports*, *16*(10), 490. https://doi.org/10.1007/s11920-014-0490-8
48. Zwecker, M., Sarova, I., Lavie, M., Zeilig, G., & Achiron, A. (2018). Detection of Cognitive

Impairment in Multiple Sclerosis Based on P300 Event-Related Potential. *International Journal of Physical Medicine & Rehabilitation*, *06*(04). https://doi.org/10.4172/2329-9096.1000479

Appendices

Appendix 1

Communalities

	Initial	Extraction
CLOX1.1	1.000	.428
CLOX1.2	1.000	.483
CLOX1.3	1.000	.385
CLOX1.4	1.000	.556
CLOX1.5	1.000	.630
CLOX1.6	1.000	.507
CLOX1.7	1.000	.420
CLOX1.8	1.000	.672
CLOX1.9	1.000	.747
CLOX1.10	1.000	.642
CLOX1.11	1.000	.465
CLOX1.12	1.000	.594
CLOX1.13	1.000	.601
CLOX1.14	1.000	.691
CLOX1.15	1.000	.417

Appendix 2

Communalities

	Initial	Extraction
CLOX2.1	1.000	.839
CLOX.2.2	1.000	.894
CLOX2.3	1.000	.844
CLOX2.4	1.000	.608
CLOX2.5	1.000	.507
CLOX2.6	1.000	.363
CLOX2.7	1.000	.581
CLOX2.8	1.000	.615
CLOX2.9	1.000	.695
CLOX2.10	1.000	.763
CLOX2.11	1.000	.626
CLOX2.12	1.000	.641
CLOX2.13	1.000	.656
CLOX2.14	1.000	.502
CLOX2.15	1.000	.754

Appendix 3

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CLOX

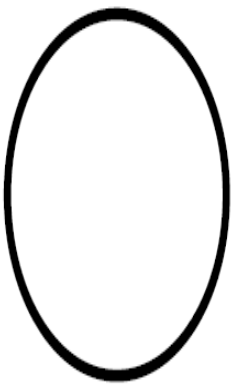
CLOX: Εκτέλεση Δοκιμασία Σχεδίασης Ρολογιού

Ονοματεπώνυμο:..... Ημερομηνία:.....

ΒΗΜΑ 1: Γυρίστε τη σελίδα προς την κενή επιφάνεια έτσι ώστε ο παρακάτω κύκλος να είναι ορατός. Ζητήστε από τον/την συμμετέχοντα/ούσα να σχεδιάσει ένα ρολόι στο πίσω μέρος. Δώστε τις εξής πληροφορίες: «Σχεδιάσετε ένα ρολόι που να δείχνει την ώρα 1:45. Βάλτε τούς δείκτες και τους αριθμούς στην επιφάνεια του ρολογιού έτσι ώστε ένα παιδί να μπορεί να τα διαβάσει». Επαναλάβετε τις οδηγίες μέχρι να γίνουν κατανοητές. Μόλις ο/η συμμετέχων/ούσα αρχίσει να σχεδιάζει, δεν επιτρέπεται περαιτέρω βοήθεια. Βαθμολογήστε αυτό το ρολόι (CLOX 1).

ΒΗΜΑ 2: Επιστρέψτε σε αυτήν την πλευρά της σελίδας, σχεδιάστε ένα ρολόι στον παρακάτω κύκλο ενώ ο/η συμμετέχων/ούσα σας παρακολουθεί. Τοποθετήστε πρώτα τα 12, 6, 3 και 9. Συμπληρώστε τους υπόλοιπους αριθμούς. Οι δείκτες να δείχνουν "1:45". Κάντε τους δείκτες σαν βέλη. Ο δείκτης που δείχνει την ώρα να είναι πιο μικρός. Ζητήστε στον/η συμμετέχων/ούσα να αντιγράψει το ρολόι στην κάτω δεξιά γωνία. Βαθμολογήστε αυτό το ρολόι (CLOX 2).

Αξιολόγηση			
Κατευθυντήρια Στοιχεία	**Βαθμοί**	**CLOX 1**	**CLOX 2**
Το σχήμα μοιάζει με ρολόι ;	1		
Υπάρχει ο εξωτερικός κύκλος ;	1		
Διάμετρος > 2,5 cm ;	1		
Όλοι οι αριθμοί μέσα στον κύκλο ;	1		
Αν υπάρχουν λάθη στις αποστάσεις, σημεία διόρθωσης η διαγραφής ;	1		
12, 6, 3, 9, μπήκαν πρώτα ;	1		
Υπάρχουν σωστές αποστάσεις, είναι συμμετρικές εκατέρωθεν του άξονα 12-6 ;	1		
Αν υπάρχουν λάθη στις αποστάσεις, υπάρχουν σημεία διόρθωσης η διαγραφής ;	1		
Μόνο αραβικοί αριθμοί ;	1		
Μόνο οι αριθμοί 1-12 μεταξύ των αριθμών:(αγνοήστε τη σημειογραφία)	1		
Η διαδοχή των αριθμών 1-12 σωστή (χωρίς παραλήψεις ή προσθήκες) ;	1		
Μόνο 2 δείκτες ;(αγνοήστε την ταξινόμηση / σημάδια διόρθωσης)	1		
Οι δείκτες ζωγραφίστηκαν σαν βέλη ;	1		
Ο ωροδείκτης είναι ανάμεσα στο 1 και το 2 ;	1		
Ο λεπτοδείκτης μεγαλύτερος από τον ωροδείκτη ;	1		
Κανένα από τα παρακάτω: 1) Δείκτης να δείχνει το 4 ή το 5	1		
2) Γράφτηκε "1:45"			
3)Οποιαδήποτε άλλη σημειογραφία (π.χ. "9:00");			
4)Τα βέλη δείχνουν προς τα μέσα;			
5) Παρεμβολές από το "δείκτες" και "όψη"			
6)Υπάρχουν λέξεις, γράμματα ή άσχετες εικόνες			
7) Στοιχεία από τον κάτωθεν κύκλο	**ΣΥΝΟΛΟ**		



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Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

Copyright

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Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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