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NEUROFEEDBACK AS AN EFFECTIVE TREATMENT FOR TICS IN ADOLESCENTS WITH TOURETTE SYNDROME: A SYSTEMATIC REVIEW

by
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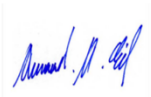

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ABSTRACT
OF THE THESIS OF

Jean-Paul Georges Saliba for Master of Science
Major: Neuroscience

Title: Neurofeedback as An Effective Treatment for Tics in Adolescents with Tourette Syndrome: A Systematic Review

Introduction: Tourette Syndrome is characterized by the pivotal presence of motor and vocal tics. It is a neurodevelopmental disorder reflecting individual-dependent tics that are described by severity, frequency, localization of speech, and fluctuation. Electroencephalography of patients with Tourette Syndrome showed a reduced sensorimotor rhythm with an excessive fronto-central theta activity, both considered as a main cause of motor and cognitive disturbances.

Objective: Several studies revealed the crucial role of neurofeedback also known as EEG Biofeedback in reducing tics in patients diagnosed with Tourette Syndrome. The current systematic review tackles the effectiveness of Neurofeedback therapy in reducing tics in adolescents with Tourette Syndrome to be more precise.

Methods: Three databases (Medline, Embase, and APA PsycINFO) were used to search for studies that included adolescents with Tourette Syndrome who received Neurofeedback as a treatment for reducing tics, with no restriction by language. For all records, titles and abstracts were screened and full texts reviewed by two reviewers to minimize the risk of bias; thus, data was extracted.

Results/Future Perspectives: The current systematic review discussed and highlighted positive outcomes when it comes to the role of neurofeedback in reducing tics in adolescents with Tourette Syndrome. Various meta-analyses showed a high clinical effectiveness of neurofeedback in reducing tics in children with Tourette Syndrome. Nevertheless, a limited and restricted number of studies tackling adolescents and adults are found. Hence, further studies on adolescents shall be conducted.

Keywords: Neurofeedback; EEG Biofeedback; Neurodevelopmental Disorders; Tics; Motor Tics; Vocal Tics; Adolescents; Tourette Syndrome; Gilles de la Tourette Syndrome; Sensorimotor rhythm; Theta activity.

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ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
CBIT	Comprehensive Behavioral Intervention for Tic Disorders
CM	Centromedian nucleus
CSTC	Cortico-Striatal-Thalamocortical Circuits
DBS	Deep Brain Stimulation
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition
EEG	Electroencephalography
FDA	Food and Drug Administration
GPe	Globus Pallidus externa
GPi	Globus Pallidus interna
HEG	Hemoencephalographic Neurofeedback
HRT	Habit Reversal Therapy
JBI	Joanna Briggs Institute
LENS	Low-Energy Neurofeedback System
LORETA	Low-Resolution Electromagnetic Tomography
NFB	Neurofeedback
OCB	Obsessive-Compulsive Behavior
OCD	Obsessive-Compulsive Disorder
SCP-NF	Slow Cortical Potential Neurofeedback
SMR	Sensorimotor Rhythm
SMA	Supplementary Motor Area
SNr	Substantia Nigra pars reticulata
STN	Subthalamic Nucleus
TS	Tourette Syndrome
USA	United States of America
YGTSS	Yale Global Tic Severity Scale

CHAPTER I

INTRODUCTION

Tics are repeated uncontrolled sudden movements, twitches, and vocal sounds that a person does. People might present tic disorders, starting from motor tics such as blinking to vocal tics that can take the form of making a grunting sound unwillingly. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association, 2013), three tic disorders are highlighted: Tourette Syndrome, Persistent or Chronic Motor or Vocal Tic Disorder, and Provisional Tic Disorder. People with Tourette Syndrome (TS) have both motor and vocal tics. However, TS is considered a neurodevelopmental disorder requiring that the patient has to have tic symptoms for at least one year (Centers for Disease Control and Prevention, 2020). The recording of scalp electroencephalography in patients with Tourette Syndrome came out with additional and complementary information for scientists to understand brain dysfunctions in the abovementioned disorder (Benvenuti et al., 2011). Despite the fact that the main treatment of Tourette Syndrome resides in dopamine blocking medications aiming to decrease the frequency and severity of tics (Robertson, 2000), plenty of behavioral therapeutic strategies target the enhancement of voluntary control over both motor and vocal tics (Himle et al., 2006). Having said that, neurofeedback or EEG biofeedback is strongly considered as an adequate and potentially effective intervention for Tourette Syndrome. Nevertheless, few studies are conducted to test its clinical effectiveness, especially when it comes to adolescents.

CHAPTER II

TOURETTE SYNDROME

A. General Overview

Tourette Syndrome is a neurodevelopmental disorder known for its repetitive motor and vocal tics. Severity, frequency, fluctuation, and localization of speech and tics are individual-dependent. After performance of tics, an inner tension breaks out, and the person feels relieved. Various comorbidities may exist such as Attention Deficit Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), depression, learning difficulties/disabilities, and self-injurious behavior (Burd et al., 2005; Gunduz & Okun, 2016). Although accompanied with significant side effects, classical antipsychotics such as Haloperidol and Pimozide have been considered as a first-choice treatment for tics. Various novel effective therapies show promising results in reducing tics in patients such as Neurofeedback (Zhuo & Li Li, 2014).

B. Epidemiology

Tourette Syndrome's symptoms begin in childhood, with an estimated prevalence of 3 to 9/1000 children, knowing that maximal severity is between the age of 10 and 12 years old. Moreover, the first episode of motor tics usually appears at an age average of 4 to 6 years old, with a sex ratio of 3/4:1, connotating a more common appearance in boys. Furthermore, vocal tics follow motor ones. The majority of patients show a full or nearly complete remission of Tourette Syndrome after the age of 21 years old. Only 10 to 20% present a fluctuation in TS symptoms that can either persist or worsen. Unfortunately, sniffing and coughing tend to be mistakenly taken for allergies at first; thus, Tourette Syndrome might be misdiagnosed (Cath et al., 2011; Robertson et

al., 2017). Before appearance of tics, patients often present ADHD. Additionally, OCD appears with its first symptoms several years after the beginning of TS tics with a high severity in late adolescence. Having said that, it is good to know that the abovementioned psychiatric comorbidities usually persist even until adulthood, despite the remission of Tourette Syndrome (Gunduz & Okun, 2016; Hirschtritt et al., 2015).

C. Etiology

Genetic and nongenetic factors participate together in the development of Tourette Syndrome, taking into account the presence of several different genes that are involved, making TS a polygenic hereditary disorder. The main cause of Tourette Syndrome is still unknown, despite the fact that chromosomal aberrations rarely occur. In many family studies, a history of tics is highlighted in the majority of parents (Scharf et al., 2015). No causative gene mutation or common variant has been relevant to account for the majority of the Tourette Syndrome cases (Davis et al., 2013). In addition to the genetic component, environmental negative effects are considered to be prenatal intakes such as smoking, fetal hypoxia, infections, stress during pregnancy, and stressful events that the child may experience (Cath et al., 2011; Robertson et al., 2017). Not only external environmental factors are implicated, but also the role of infections is important, many children having experienced sinusitis develop Tourette Syndrome (Selling, 1929). Additionally, rheumatic fever associated with Sydenham's chorea show to have neurological manifestations which are tics, thing that has been suggested as a pathophysiology for Tourette Syndrome. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections have been cited and developed in many studies as well (Lin et al., 2010; Swedo et al., 1998).

D. Clinical Features

Tics are described as sudden, involuntary, nonrhythmic, repetitive and stereotyped motor movements or vocalizations that highly resemble regular motor behaviors and movements but show up out of context. Tics may involve any muscular group knowing that some of them is more frequent such as eye blinking which is often the first to emerge. Some tics are called blocking tics leading to disruption of ongoing communication or speech (Jankovic, 1997; Ganos et al., 2014).

Motor tics can be either simple (activating single muscles or localized muscle group) or complex (activating several muscles): blinking, nose twitching, and shoulder shrugging are good examples of simple motor tics, taking into account that chewing, facial and body contortions, twirling, jumping, and dystonic tics are considered complex motor tics. Concerning vocal tics, simple vocal tics refer to throat clearing, sniffing, gulping, coughing, snorting, or producing animal noises. Complex vocal tics include letter or word substitution, intonation changes, and accent imitations (Gill & Kampoliti, 2020). Involuntary repetition of one's actions or echopraxia, repeating other's vocalizations or echolalia, and repeating the last word or phrase said by a person or palilalia are very common in people with Tourette Syndrome. Echopraxia, echolalia, and palilalia are all under the big umbrella of echophenomena which is considered as normal if present in children till the age of 36 months. Some patients involuntarily make obscene gestures and present an out-of-context swearing. Coprophenomena is considered to be a sign of Tourette Syndrome severity, knowing that it is highly correlated with the severity of present tics, psychiatric comorbidities, and pharmacotherapy (Nagai et al., 2014). Although tics are involuntary, they can be voluntary suppressed by the patient, differentiating TS patients from other hyperkinetic movement disorders. After a tic suppression period, the patient might experience a

rebound release of tics that is harder than regular encountered symptoms (Jankovic, 2001). Conclusively, tics are usually exacerbated during stress, anticipation periods, and fatigue. They can be reduced when the patient is concentrating on physical and mental tasks. Some studies showed that even during sleep, tics persist (Hanna & Jankovic, 2003).

E. Pathophysiology: Neurophysiology

Neurophysiological basis concerning mechanisms of involuntary tics is emphasized through the classical models of cortico-striatal-thalamocortical circuits (CSTC), suggesting that cortical excitability via both direct and indirect basal ganglia pathways plays a major role in modulating behaviors. Direct basal ganglia pathway starts from the striatum to the globus pallidus interna (GPi) and the substantia nigra pars reticulata (SNr), exciting the cortex when disinhibiting the thalamus. Indirect basal ganglia pathway starts from the striatum to the globus pallidus externa (GPe) to the subthalamic nucleus (STN), inhibiting thalamic projections. Hence, focal aberrations in the striatum cause inhibition of the GPi and SNr in the direct basal ganglia pathway, leading to an involuntary motor command to be executed in the cortex, thus highlighting an excessive disinhibition. Additionally, deep brain stimulation surgery showed a low-frequency activity during tics in the ventralis oralis complex or centromedian nucleus (CM) of the thalamus (Novotny et al., 2018). Such activity was not detected in the thalamus during voluntary mimicking of same tics or during their suppression (Albin & Mink, 2006; Albin et al., 1989; Maling et al., 2012; Marceglia et al., 2010; Mink, 2003).

F. Pathophysiology: Neuroimaging

Several studies highlighted a smaller volume of the caudate nucleus which is linked to the severity of tics in patients with Tourette Syndrome in a longitudinal study. However, other studies showed that young adolescents with persistent tics had a decreased volume of the left putamen and diffusion alteration in the right caudate nucleus, thalamus and frontal lobe. Moreover, decreased projections between caudate nucleus and lateral frontal cortex were noted as well, supporting the theory of the cortical disinhibition for Tourette Syndrome patients, underlying aberrations in the striatum (Biermann-Ruben et al., 2012; Franzkowiak et al., 2010; Peterson et al., 2003). Nevertheless, other changes were detected outside the striatum including a reduced cortical thickness in motor, premotor, prefrontal, and lateral orbitofrontal cortical areas, structural alterations in somatosensory pathways and the corpus callosum (Bloch et al., 2005; Makki et al., 2009; Worbe et al., 2010). However, an fMRI study showed an abnormal activity of the CSTC circuits in premotor, sensorimotor, and cingulate cortices, in addition to the medial thalamus (Worbe et al., 2012).

G. Pathophysiology: Neurochemistry

Many studies highlighted the pivotal neurochemical abnormalities hypothesis of Tourette Syndrome (Singer, 1992; Swedo et al., 1992). Having said that, dopaminergic dysfunction is the most common hypothesis, knowing that most effective drugs in reducing tics are neuroleptics i.e. dopamine receptor-blocking drugs. Nevertheless, some abnormalities were detected concerning dopamine transporter binding capacity (Harris & Singer, 2006) and increases of cortical and striatal dopamine receptors (Cheon et al., 2004; Minzer et al., 2004; Serra-Mestres et al., 2004), with no dopaminergic hyperinnervation detected by PET studies (Wong et al., 1997).

H. Diagnosis of Tourette Syndrome

Generally, the diagnosis of tic disorders is delicate and demands a lot of documentation concerning the onset of the disorder in the childhood of the patient, motor and behavioral phenomenology, in addition to a neurological examination and family history information. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition – DSM-5 (American Psychiatric Association, 2013) defines diagnostical criteria of Tourette Syndrome. Criterion A tackles the presence of both motor and vocal tics, criterion B emphasizes tics' onset before the age of 18 years old. Criterion C shows the importance of tic persistence for greater than a year, and criterion D shows the importance of the elimination of potential causes of tics and other medical conditions which is pivotal prior to the diagnosis of Tourette Syndrome. Fortunately, tics can be differentiated based on patient's history, clinical examination, the capacity to suppress tics and the presence of premonitory urges in patients (Jankovic & Mejia, 2006). For an accurate diagnosis, Yale Global Tic Severity Scale (YGTSS) is used for a better knowledge concerning types of tics that are found in patients and their age of appearance (Novotny et al., 2018).

I. Treatments and Interventions

Educating the patient, his/her parents, caregivers, colleagues, and peers is pivotal for them to understand all daily basis conditions imposed by Tourette Syndrome (Jankovic, 2009; Singer, 2010). Treating Tourette Syndrome comorbidities has a crucial role in diminishing tic severity in patients (Leckman, 2002). Additionally, Tourette Syndrome can be treated via several strategies: Pharmacotherapy and behavioral

therapeutic strategies are most tackled, for the only exception of medication refractory where surgery might be applied, especially deep brain stimulation with targeted areas. Concerning behavioral therapy, Comprehensive Behavioral Intervention for Tic Disorders (CBIT) is highly effective, including the Habit Reversal Training (HRT). This behavioral approach aims to a more facilitated control of tics, thus disrupting the relief sensation after tic execution. In addition to that, a combination of CBIT with exposure and response prevention therapy might be needed especially in patients with obsessive-compulsive disorder (OCD) (Gunduz & Okun, 2016).

On the pharmacological scale, first-line treatment is the alpha agonists guanfacine and clonidine (Leckman et al., 1982; Scahill et al., 2001), for mild to moderate tics highlighting few side effects such as dry mouth and drowsiness. Neuroleptics or antipsychotic drugs are considered second-line treatment for patients with Tourette Syndrome with various side effects such as severe weight pain, excessive sedation, parkinsonism, akathisia and others (Roessner et al., 2013). However, atypical antipsychotic drugs have been preferred over typical ones, this is to mention a better adverse event profile with a lower risk of tardive dyskinesia (Peña et al., 2011). Haloperidol and Pimozide are the only FDA-approved drugs for the treatment of Tourette Syndrome (Wijemanne et al., 2014).

When the patient does not respond to any pharmacological and behavioral therapy, he/she presents malignant Tourette Syndrome, requiring the treatment of tics using deep brain stimulation (DBS) surgical intervention, treating not only tics but also associated OCD.

CHAPTER III

NEUROFEEDBACK OR EEG-BIOFEEDBACK

A. General Overview

Neurofeedback is considered to be currently an interesting subject for researchers. Patients benefiting from it control their brain waves in a conscious way while electroencephalography is being recorded during the treatment. The subject is aware and conscious of the changes occurring throughout the training, being able to evaluate his/her progress while aiming to achieve an optimal performance. Based on the changes occurring in the sound or the video, the subject targets improving the brain patterns. Concerning treatment protocol, neurofeedback focuses on alpha, beta, delta, theta, and gamma treatments, knowing that some combinations might exist, e.g. alpha/theta ratio and others (Dempster, 2012; Vernon, 2005).

B. Frequency Components

Activation of neurons produces electrical pulses that can be recorded via EEG when electrodes are placed on the scalp, showing the synchronous activity of pyramidal neurons knowing that electrical output reaches skin areas where electrodes are placed. Brain waves are always recognized by two main factors: Amplitude which shows the power of brain waves (μV) and frequency indicating wave oscillations (Hz). Every frequency component represents a well-defined physiological function, and is categorized into alpha (8-13 Hz), beta (13- 30 Hz), delta (less than 4 Hz), theta (4-8 Hz), and gamma (30-100 Hz). Alpha waves are observed when the patient is relaxed with loose muscles but awake, beta waves when the person is alert, delta waves is when

the patient is asleep, theta waves when the patient is sleepy, and gamma waves is when the person is solving a problem (Marzbani et al., 2016).

C. Electroencephalogram Display

Electrode system 10-20 aims to standardize skull areas and compare data, it refers to placing electrodes over 10% or 20% of the total distance between targeted skull locations. From 21 electrodes, 2 are used as a reference, and 19 for recording cortical areas. Letters are attributed to related brain regions and numbers to brain hemisphere: F for frontal, P for parietal, T for temporal, O for occipital and C for central areas. Odd and even numbers are related to the left and right sides of the brain region. Letter z is used as Pz suggesting that scalp location falls on the central line, between the nasion and the inion. Fp1 is related to the left pole of the forehead, while Fp2 is concerned for the right one. A1 and A2 are known for the left and right regions of the vestibular region and are common sites for placing both ground and reference electrodes (Dempster, 2012; Evans & Abarbanel, 1999). Lesions in specific brain regions have specific symptoms that are correlated to these regions. Frontal lobes are responsible for time management, social skills, emotions, empathy, executive planning, working memory, and immediate and sustained attention. Parietal lobes are responsible for complex grammar, naming of objects, construction of sentences, mathematical processing, spatial recognition, and knowing the difference between left and right. Temporal lobes are associated with reading, memory, learning, positive mood, music, anxiety, facial recognition, and direction sense. Occipital lobes are responsible for visual memories, traumatic memories, accurate reading, object location, seeing colors, spelling, and drawing recognition. Concerning sensorimotor cortex, it is responsible for

typing, playing music, handwriting, complex machinery operation, speaking, and recognition of the origin of body sensations (Demos, 2005; Evans, 2007).

D. Types of Neurofeedback

Neurofeedback is being used for the treatment of several disorders, taking into account the presence of 7 types. Frequency/power neurofeedback is the most frequently used type of neurofeedback that uses 2 to 4 electrodes to treat ADHD, insomnia, and anxiety. The second type is the Slow Cortical Potential Neurofeedback (SCP-NF) aims to improve the direction of slow cortical potentials to treat migraines, epilepsy, and ADHD (Christiansen et al., 2014). Low-Energy Neurofeedback System (LENS) with a weak electromagnetic signal delivery targets to change brain waves in patients who are motionless with closed eyes as well, in order to treat traumatic brain injury, ADHD, insomnia, restless legs syndrome, fibromyalgia, anger, depression, and anxiety (Mehran et al., 2015). The fourth neurofeedback type is called Hemoencephalographic Neurofeedback (HEG) and it aims to treat migraine via feedback on cerebral blood flow (Dias et al., 2012). Live Z-score neurofeedback is mainly used for insomnia treatment (Marzbani et al., 2016). Low-Resolution Electromagnetic Tomography (LORETA) uses 19 electrodes in order to treat Obsessive-Compulsive Disorder, addictions, and depression (Pascual-Marqui et al., 1994). Concerning the most recent type of neurofeedback, it is about fMRI that stands for functional magnetic resonance imaging, aiming to regulate the brain activity via feedback from subcortical areas of the brain (Hurt et al., 2014).

E. Clinical Applications of Neurofeedback

Neurofeedback training has various clinical applications when it comes to treatment of diseases and disorders. Patients with ADHD, schizophrenia, insomnia, learning difficulties/disabilities, developmental disabilities, drug addiction and alcoholism, autism spectrum disorder, epilepsy, depression, anxiety, pain management, traumatic brain injury and stroke, antisocial personality, posttraumatic stress disorder, and headaches and migraines benefit from neurofeedback treatment (Marzbani et al., 2016; Hammond, 2011). However, recent studies show that neurofeedback has a crucial role at enhancing sensorimotor rhythm in patients with tic disorders, knowing that patients with Tourette syndrome reveal a reduced sensorimotor rhythm and excessive fronto-central theta activity, main cause of motor and cognitive disturbances (Benvenuti et al., 2011). Additionally, neurofeedback is currently considered as a potential therapy for patients with Tourette syndrome, knowing that Tourette Syndrome shares symptoms or comorbid diagnoses of OCD and ADHD (Benvenuti et al., 2011; Gevensleben et al., 2014; Tansey, 1986).

CHAPTER IV

METHODS

A. Search Strategy and Article Selection Criteria

Prospective submission of the systematic review protocol was made on PROSPERO (CRD42021258156). PRISMA reporting guidelines were adopted in this review (Moher et al., 2009).

From database inception to May 8, 2021, we searched for studies of any design with no restriction by language, that included adolescents (10-19 years old according to WHO) diagnosed with Tourette Syndrome and have already benefited from Neurofeedback therapy (NFB) to reduce tics. Adolescents presenting comorbidities such as Obsessive-Compulsive Disorder (OCD), Obsessive Compulsive Behavior (OCB) and Attention Deficit Hyperactivity Disorder (ADHD) are included in this study. The aim of the current systematic review is to investigate the effectiveness of Neurofeedback (or EEG-Biofeedback) in reducing tics in adolescents with Tourette Syndrome.

Three databases were used to search for relevant studies, MEDLINE (using the Ovid platform) (appendix A), Embase (appendix B), and APA PsycINFO (using the Ovid platform) (appendix C). We looked manually for grey literature using Scopus to broaden our search and get more records included in this review. No relevant data was highlighted after performing both backward and forward citation tracking to identify further eligible studies. We could not obtain 10 full texts, but we obtained 8 of them via the pivotal help of the medical librarian at the American University of Beirut.

B. Data Collection

Two reviewers assessed in duplicates and independently titles and abstracts of already identified citations. Full texts of eligible citations were obtained. One article was the only difference between both reviewers, hence the disagreement was resolved by simple discussion. Details about obtained citations and reasons for exclusion are summarized using a PRISMA flow diagram. We assessed the risk of bias of three case report studies (Benvenuti et al., 2011; Zhuo & Li Li, 2014; Tansey, 1986) using the JBI Critical Appraisal Checklist for Case Reports (Appendix E) (Moola et al., 2017), and the Cochrane Collaboration's Tool for assessing risk of bias (Appendix F) (Higgins & Altman, 2008) for only one randomized controlled study (Sukhodolsky et al., 2020). Included studies reflected a low risk of bias. We extracted data for study design, population characteristics, intervention type, outcomes, and results.

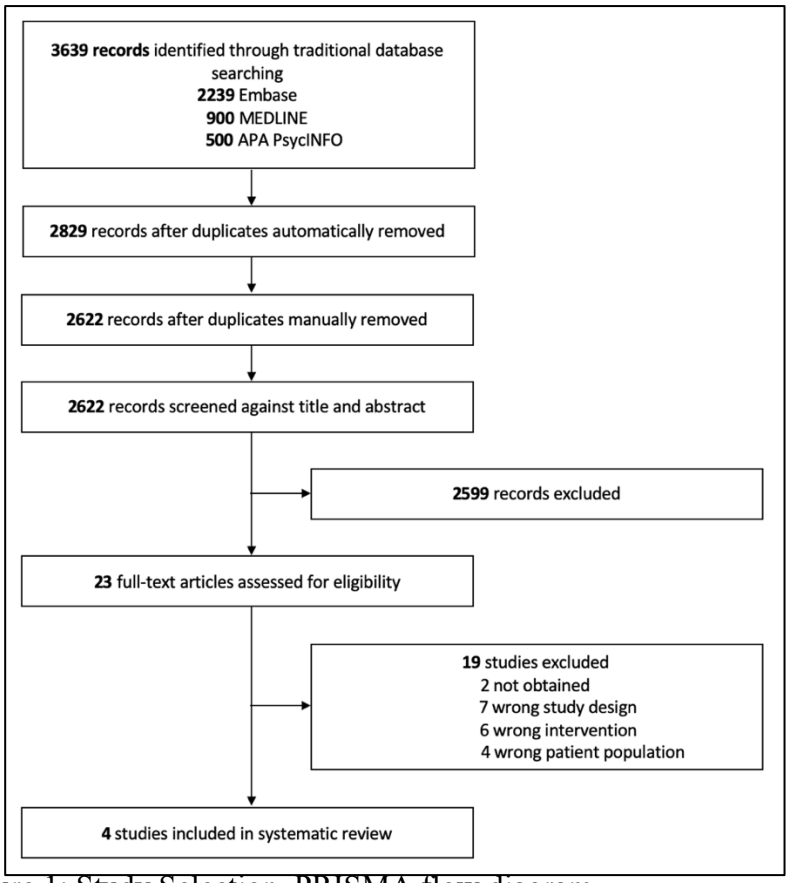

Figure 1: Study Selection, PRISMA flow diagram

Table 1: Characteristics of included studies

	Study Type	Sample Size (n)	Age	Country	Diagnosis	Comorbidities	Medication during NFB	Outcomes	Results
Messerotti Benvenuti, Buodo, Leone &Palomba (2011)	Uncontrolled Single Case Study	1	Male: 17	Italy	Tourette Syndrome	• OCD • Borderline Intellectual Functioning	• Pimozide (Orap) *12mg/day* • Valproate (Depakin) *250 mg/day*	• Sensorimotor rhythm amplitude (SMR) • Theta activity amplitude	• SMR power increased at Cz (top) • Theta power decreased at C4 (bottom) • Significant reduction for the frequency of non-obscene vocal tics and frequency and severity of obscene motor tics.
Sukhodolsky et al (2019)	Randomized Sham-Controlled Study	21	11-19	USA	Tourette Syndrome	• Depression • Anxiety • OCD • ADHD	Only for patients whose medication was stable for at least 1 month before baseline with no planned changes during trial (psychotropic medications)	• Supplementary Motor Area Activity (SMA) • Tic Severity	• Reduction of tic severity • No significant results concerning SMA
Tansey (1986)	Case-Report	1	Male: 14	USA	Tourette Syndrome	-	No	Sensorimotor rhythm (SMR)	• Mean amplitude of SMR increased 21% over baseline • Average amplitude of 6-8 Hz brainwave activity de- creased by 16.8% • Tic cessation and ADHD symptoms for 6 months
Zhuo & Li Li (2014)	Case-Report	2	Female: 14	China	Tourette Syndrome	-	No	Tic symptoms	Significant improvement in tic symptoms
			Male: 16			-	Haloperidol 5,5 mg/day		

USA=United States of America. **OCD**=Obsessive-Compulsive Disorder. **ADHD**=Attention Deficit Hyperactivity Disorder. **SMA**=Supplementary Motor Area. **SMR**=Sensorimotor Rhythm

C. Outcomes

In the current systematic review, outcomes of interest were sensorimotor rhythm (SMR), theta activity, and tic severity (motor and vocal tics). Patients diagnosed with Tourette Syndrome usually present with a reduced sensorimotor rhythm and an excessive fronto-central theta activity main cause of motor and cognitive disturbances leading to the presence of motor and vocal tics.

CHAPTER V

RESULTS

A total of 3639 studies were identified through traditional database searching, of which 4 met the inclusion criteria; see Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) inclusion flow diagram and Table 1 for the characteristics of the four included studies. Two of the reports are case-reports studies (Zhuo & Li Li, 2014; Tansey, 1986), one is a randomized sham-controlled study (Sukhodolsky et al., 2020), and one is an uncontrolled single case study (Benvenuti et al., 2011). Studies were all experimental where neurofeedback therapy was present. The first study (Benvenuti et al., 2011) focused on both sensorimotor rhythm (SMR) and theta activity, the second (Tansey, 1986) dealt with sensorimotor rhythm (SMR) only, the third (Sukhodolsky et al., 2020) tackled the supplementary motor area (SMA) and tic severity, and the fourth study (Zhuo & Li Li, 2014) focused on tic symptoms as a main pivotal outcome. All studies included Tourette Syndrome (TS) diagnosed patients. In some studies, patients were taking medications such as Haloperidol, Pimozide (Orap), Valproate (Depakin), and other psychotropic medications (Benvenuti et al., 2011; Zhuo & Li Li, 2014; Sukhodolsky et al., 2020). All abovementioned studies demonstrated significant improvements in adolescents with Tourette Syndrome such as an increased sensorimotor rhythm activity, reduced theta activity, and a reduction of tic severity according to the Yale Global Tic Severity Scale (YGTSS). Three studies (Benvenuti et al., 2011; Tansey, 1986; Sukhodolsky et al., 2020) showed neurofeedback as the only intervention for adolescents with Tourette Syndrome, and one study (Zhuo & Li Li, 2014) combined neurofeedback therapy with imagery training for better maintained outcomes; we did not exclude this study because imagery training aimed to

maintain effects of neurofeedback in patients instead of treating tics. Hence, imagery training was considered pivotal for the maintenance of the positive effects of neurofeedback therapy in reducing tic symptoms.

In the study of Benvenuti and his colleagues (2011), the patient had been treated unsuccessfully with Pimozide (Orap) and Sodium Valproate (Depakin) for 7 years and he did not discontinue medication during neurofeedback. After completion of the neurofeedback protocol, sensorimotor rhythm power increased at Cz, and theta power decreased at C4. Additionally, a significant reduction in the frequency of non-obscene vocal tics and frequency and severity of obscene motor tics was highlighted as well. The study of Tansey (1986) showed that the mean amplitude of sensorimotor rhythm increased by 21% over the baseline, the patient showed tic cessation and remained free from tics and attention deficit disorder's constellation of symptoms at a 6-month follow up. Sukhodolsky and colleagues (2020) highlighted a reduction in tic severity in adolescents after being exposed to neurofeedback therapy sessions; some of them, who have their psychotropic medication stable for at least one month before baseline, did not discontinue taking it during neurofeedback therapy. Adolescents receiving real neurofeedback had greater reduction of tics compared with the sham control: Mean Yale Global Tic Severity Scale Total Tic (YGTSS) (Appendix D) (Leckman et al., 1989) score decreased from 25.2 ± 4.6 at baseline to 19.9 ± 5.7 at end point in the neurofeedback condition and from 24.8 ± 8.1 to 23.3 ± 8.5 in the sham control condition, highlighting the meaningful effectiveness of the neurofeedback therapy in reducing tic severity in adolescents with Tourette Syndrome. In their study, Zhuo and Li Li (2014) presented two adolescents with Tourette Syndrome, the girl used to take medications such as Tiapride, Haloperidol, Aripiprazole, and Olanzapine showing undesired side effects and/or no significant improvement in tic symptoms and all

medications were withdrawn. The boy is currently taking a low dosage of Haloperidol as a treatment for his tics, knowing that he experienced undesired side effects when his doctor tried to increase dosage for his tics were still present. For the girl, overall severity score was reduced from 87 to 50 points, with tic severity score reduced from 46 to 28 points according to the Yale Global Tic Severity Score. For the boy, overall severity score was reduced from 73 to 40 points, with tic severity score reduced from 38 to 25 points. All abovementioned studies showed neurofeedback as a promising treatment or addition to drug-therapy for adolescents presenting with a medication-refractory Tourette Syndrome.

CHAPTER VI

DISCUSSION

A. Summary of Findings

We systematically reviewed literature for the effectiveness of neurofeedback therapy in reducing tics in adolescents diagnosed with Tourette Syndrome. Participants in included studies showed an increased sensorimotor rhythm activity (SMR uptraining), a decreased theta activity (theta downtraining), hence a significant reduction of motor and vocal tics after neurofeedback therapy sessions.

Neurofeedback turned to be a pivotal treatment when adolescents present with medication-refractory Tourette Syndrome, or even an alternative or addition to drug-therapy itself. Even when neurofeedback is accompanied with imagery training, positive effects of neurofeedback are obviously significant, thus maintained by imagery training.

B. Strengths and Limitations of Current Review

To our knowledge, this is the first study to review literature for the effectiveness of neurofeedback therapy in reducing tics in adolescents with Tourette Syndrome. The Cochrane Collaboration Methodology for conducting systematic reviews was our crucial guide throughout the whole study. We started with the search strategy using three databases, duplicate and independent selection and data collection processes.

Results of the current systematic review should be interpreted in line with its limitations. Some studies included participants using medications for tic reduction purposes, which may influence the effectiveness of neurofeedback as a treatment for reducing tics in adolescents with Tourette Syndrome. Nevertheless, the number of included studies is relatively restricted, thus finding adequate studies including

adolescents diagnosed with Tourette Syndrome is considered a heavy limitation for this review. Not only an effective treatment for vocal and motor tics, neurofeedback can be considered a valuable addition to drug-therapy as well. Number of studies and population size influences outcomes of the current review. More randomized controlled trials (RCTs) with longer follow-up on adolescents with Tourette Syndrome who received neurofeedback sessions are mandatory before definite conclusions can be drawn, knowing that the majority of included studies are case reports. Future studies including participants using and not using medications for tic reduction are pivotal for more precise outcomes when it comes to sample size and medications. Additionally, included studies were conducted in Non-Arab countries, thus limiting the generalizability of their findings.

CHAPTER VII

CONCLUSION

To sum up, the current review discussed the pivotal role of neurofeedback (NFB) in SMR uptraining, theta activity downtraining, and reducing tics in adolescents diagnosed with Tourette Syndrome (TS). This syndrome is more common in boys and reveals motor tics followed by vocal tics. Knowing that genetic and nongenetic factors participate in the development of the Tourette Syndrome, it is suggested that involuntary tic mechanisms are related to cortical excitability through direct and indirect basal ganglia pathways (Cortico-Striatal- Thalamocortical Circuits): Disinhibited thalamus and inhibited thalamic projections respectively. However, various meta-analyses showed the high clinical effectiveness of neurofeedback in reducing tics in children with Tourette Syndrome, taking into account a very small number of studies talking about adolescents and adults. Having said that, abovementioned studies pointed out promising results concerning neurofeedback or EEG-biofeedback in increasing sensorimotor rhythm activity, decreasing theta activity, and reducing tics in adolescents with Tourette Syndrome. Hence, further studies must be conducted for better outcome quality and clinical reliability.

APPENDIX

A. Search Strategy using MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-
Search Strategy:

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1 Neurofeedback/ (1031)
2 Neurological Rehabilitation/ (1082)
3 (((alpha or brainwave? or (brain adj wave?) or electrom?ogra* or (electro adj m?ogra*) or electroencephalogr* or (electro adj encephalogr*)) adj3 (feedback? or (feed adj back?) or biofeedback? or (bio adj feedback?))) or neurofeedback? or (neuro adj feedback?) or (neurofeed adj back) or (neuro adj feed adj back) or neurobiofeedback or neuro-biofeedback or neurotherap* or neuro-therap* or neurorehabilit* or neuro-rehabilit* or (neuro* adj rehabilita*)).mp. (9709)
4 Electroencephalography/ (148930)
5 (eeg? or electroencephalogra* or (electro adj encephalogra*) or (electrical adj1 activit*)).mp. (197965)
6 exp Brain Waves/ (15034)
7 ((rhythm? adj3 (alpha or alfa or bet?a or delta or gam?a or t?eta or mu)) or brainwave? or (brain adj wave?)).mp. (18599)
8 Biofeedback, Psychology/ (7362)
9 (((feedback? or (feed adj back*) or biofeedback? or (bio adj feedback?) or (biofeed adj back) or (bio adj feed adj back)) adj3 (bogus or false or psyc?oph?siolog* or (psyc?o adj ph?siolog*) or psyc?olog*)) or m?ofeedback* or (m?o adj feedback*) or (m?ofeed adj back) or (m?o adj feed adj back)).mp. (11337)
10 Feedback, Psychological/ (3609)
11 ((feedback? adj1 psyc?olog*) or (feed-back adj1 psyc?olog*)).mp. (3623)
12 exp Electroencephalography Phase Synchronization/ (3510)
13 ((s?nc?ron* or de-s?nc?ron* or des?nc?ron*) adj3 (cortex or cortical or cortices)).mp. (4158)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (223008)
15 Tourette Syndrome/ (4399)
16 Neurodevelopmental Disorders/ (2834)
17 ((tourette* or tourete* or toorette* or toorete* or (neuro adj1 develop?ment*) or neurodevelop?ment* or tic?) adj3 (disease? or disorder? or syndrom* or il?ness* or sickness*)).mp. (28593)
18 Tics/ (940)
19 ((tic? or spasm* or chorea?) adj3 (gestur* or motor* or motricit* or transient or vocal* or habit* or facial or nervous)).mp. (2488)
20 Tic Disorders/ (1618)
21 ((tic?-disorder? or tic?) adj3 (vocal* or transient* or motor* or motricit* or posttraumatic or (post adj traumatic) or child*)).mp. (1731)
22 Echolalia/ (225)
23 (((ec?olal* or ec?oph*) adj3 (spe?ch* or reaction?)) or ec?olal* or ec?ophenomen* or (ec?o adj1 answer*) or ec?oprax* or coprolal* or coproprax* or pal?ilal*).mp. (643)
24 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (30593)

25	14 and 24 (900)

Table 2: Search strategy using MEDLINE database

B. Search Strategy using Embase

No. Query	Results
#30 #**21** AND #**29**	**2,239**
#29 #**22** OR #**23** OR #**24** OR #**25** OR #**26** OR #**27** OR #**28**	**41,160**
#28 (((ec$olal* OR ec$oph*) NEAR/3 (spe$ch* OR reaction$)):ti,ab,kw) OR ec$olal*:ti,ab,kw OR ec$ophenomen*:ti,ab,kw OR 'ec$o* near/1 answer*':ti,ab,kw OR **'eco answers'**:ti,ab,kw OR **'echo answer'**:ti,ab,kw OR **'echo answers'**:ti,ab,kw OR ec$oprax*:ti,ab,kw OR **coprolal***:ti,ab,kw OR **coproprax***:ti,ab,kw OR pal$ilal*:ti,ab,kw	**824**
#27 **'echolalia'**/de OR **'echopraxia'**/de OR **'coprolalia'**/de OR **'copropraxia'**/de OR **'palilalia'**/de	**892**
#26 (('tic$-disorder$' OR tic$) NEAR/3 (**vocal*** OR **transient*** OR **motor*** OR **motricit*** OR **posttraumatic** OR **'post next/1 traumatic'** OR **child***)):ti,ab,kw	**2,480**
#25 ((tic$ OR **spasm*** OR chorea$ OR **twitch***) NEAR/3 (**gestur*** OR **motor*** OR **motricit*** OR **transient** OR **vocal*** OR **habit*** OR **facial** OR **nervous**)):ti,ab,kw	**4,268**
#24 **'tic'**/de	**8,524**
#23 ((**tourette*** OR **tourete*** OR **toorette*** OR **toorete*** OR 'neuro near/1 develop$ment*' OR neurodevelop$ment* OR tic$) NEAR/3 (disease$ OR disorder$ OR **syndrom*** OR il$ness* OR **sickness***)):ti,ab,kw	**31,450**
#22 **'gilles de la tourette syndrome'**/de	**8,550**
#21	**305,035**

#1 OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20**

1,842

#20
((sncron* OR 'de-sncron*' OR desncron*) NEAR/3 (**cortex** OR **cortical** OR **cortices**)):ti,ab,kw

1,140

#19
'electroencephalography phase synchronization'/de

25

#18
((feedback$ NEAR/1 psyc$olog*):ti,ab,kw) OR ((**'feed back'** NEAR/1 psyc$olog*):ti,ab,kw)

396

#17
'psychological feedback'/de

60

#16
m$ofeedback*:ti,ab,kw OR **'myo feedback'**:ti,ab,kw OR **'myo feedbacks'**:ti,ab,kw OR **'myofeed back'**:ti,ab,kw OR **'myofeed backs'**:ti,ab,kw OR **'myo feed back'**:ti,ab,kw OR **'myo feed backs'**:ti,ab,kw

721

#15
((feedback$ OR **'feed back'** OR **'feed backs'** OR biofeedback$ OR **'bio feedback'** OR **'bio feedbacks'** OR **'biofeed back'** OR **'biofeed backs'**OR **'bio feed back'** OR **'bio feed backs'**) NEAR/3 (**bogus** OR **false** OR psycophsiolog* OR **'psycho physiolog*'** OR **'psyco physiolog*'** OR **'psyco phisiolog*'** OR **'psycho phisiolog*'** OR psyc$olog*)):ti,ab,kw

22

#14
'biofeedback training'/de

2,429

#13
'biofeedback'/de

9,927

#12
((rhythm$ NEAR/3 (**alpha** OR **alfa** OR bet$a OR **delta** OR gam$a OR t$eta OR **mu**)):ti,ab,kw) OR brainwave$:ti,ab,kw OR **'brain wave'** OR **'brain waves'**:ti,ab,kw

3,641

#11
'cortical synchronization'/de

23,576

#10

'alpha rhythm'/de OR **'beta rhythm'**/de OR **'theta rhythm'**/de OR **'gamma rhythm'**/de OR **'mu rhythm'**/de OR **'delta rhythm'**/de OR **'hippocampus theta rhythm'**/de

110,647

#9
'electroencephalogram'/de

181,584

#8
eeg$:ti,ab,kw OR **electroencephalogra***:ti,ab,kw OR **'electro encephalogram'**:ti,ab,kw OR **'electro encephalograms'**:ti,ab,kw OR **'electro encephalography'**:ti,ab,kw OR **'electro encephalographies'**:ti,ab,kw OR **'electro encephalograph'**:ti,ab,kw OR **'electro encephalographs'**:ti,ab,kw OR **'electrical-activit*'**:ti,ab,kw

1,384

#7
'electroencephalography monitoring'/de

129,016

#6
'electroencephalography'/de

12,220

#5
neurofeedback$:ti,ab,kw OR **'neuro feedback'**:ti,ab,kw OR **'neuro feedbacks'**:ti,ab,kw OR **'neurofeed back'**:ti,ab,kw OR **'neuro feed back'**:ti,ab,kw OR **neurobiofeedback**:ti,ab,kw OR **'neuro biofeedback'**:ti,ab,kw OR **neurotherap***:ti,ab,kw OR **'neuro therap*'**:ti,ab,kw OR **neurorehabilit***:ti,ab,kw OR **'neuro rehabilit*'**:ti,ab,kw OR **'neuro rehabilitation'**:ti,ab,kw OR **'neuro rehabilitations'**:ti,ab,kw OR **'neuro rehabilitative'**:ti,ab,kw OR **'neurological rehabilitation'**:ti,ab,kw OR **'neurological rehabilitations'**:ti,ab,kw

1,244

#4
((**alpha** OR brainwave$ OR **'brain wave'** OR **'brain waves'** OR electrom$ogra* OR **'electro myogram'** OR **'electro myograms'** OR **'electro myography'** OR **'electro myographies'** OR **'electro myograph'** OR **'electro myographs'** OR **electroencephalogr*** OR **'electro encephalography'** OR **'electro encephalographies'** OR **'electro encephalogram'** OR **'electro encephalograms'**) NEAR/3 (feedback$ OR **'feed back'** OR **'feed backs'** OR biofeedback$ OR **'bio feedback'** OR **'bio feedbacks'**)):ti,ab,kw

5,246

#3
'neurorehabilitation'/de

27

#2
'neurotherapy'/de

3,261

#1

'neurofeedback'/de

Table 3: Search strategy using Embase database

C. Search Strategy using APA PsycINFO

S29	S19 AND S28 (500 results)
S28	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
S27	TI ((((ec#olal* OR ec#oph*) N2 (spe#ch* OR reaction#)) OR ec#olal* OR ec#ophenomen* OR ‘ec#o* answer* OR ec#o-answer* OR ec#oprax* OR coprolal* OR coproprax* OR pal#ilal*)) OR AB ((((ec#olal* OR ec#oph*) N2 (spe#ch* OR reaction#)) OR ec#olal* OR ec#ophenomen* OR ‘ec#o* answer* OR ec#o-answer* OR ec#oprax* OR coprolal* OR coproprax* OR pal#ilal*)) OR SU ((((ec#olal* OR ec#oph*) N2 (spe#ch* OR reaction#)) OR ec#olal* OR ec#ophenomen* OR ‘ec#o* answer* OR ec#o-answer* OR ec#oprax* OR coprolal* OR coproprax* OR pal#ilal*))
S26	DE "Echolalia"
S25	TI (((tic#-disorder# OR tic#) N2 (vocal* OR transient* OR motor* OR motricit* OR posttraumatic OR (post W0 traumatic) OR child*))) OR AB (((tic#-disorder# OR tic#) N2 (vocal* OR transient* OR motor* OR motricit* OR posttraumatic OR (post W0 traumatic) OR child*))) OR SU (((tic#-disorder# OR tic#) N2 (vocal* OR transient* OR motor* OR motricit* OR posttraumatic OR (post W0 traumatic) OR child*)))
S24	TI (((tic# OR spasm* OR chorea# OR twitch*) N2 (gestur* OR motor* OR motricit* OR transient OR vocal* OR habit* OR facial OR nervous))) OR AB (((tic# OR spasm* OR chorea# OR twitch*) N2 (gestur* OR motor* OR motricit* OR transient OR vocal* OR habit* OR facial OR nervous))) OR SU (((tic# OR spasm* OR chorea# OR twitch*) N2 (gestur* OR motor* OR motricit* OR transient OR vocal* OR habit* OR facial OR nervous)))
S23	DE "Tics"
S22	TI (((tourette* OR tourete* OR toorette* OR toorete* OR (neuro N0 develop#ment*) OR neurodevelop#ment* OR tic#) N2 (disease# OR disorder# OR syndrom* OR il#ness* OR sickness*))) OR AB (((tourette* OR tourete* OR toorette* OR toorete* OR (neuro N0 develop#ment*) OR neurodevelop#ment* OR tic#) N2 (disease# OR disorder# OR syndrom* OR il#ness* OR sickness*))) OR SU (((tourette* OR tourete* OR toorette* OR toorete* OR (neuro N0 develop#ment*) OR neurodevelop#ment* OR tic#) N2 (disease# OR disorder# OR syndrom* OR il#ness* OR sickness*)))

S21	DE "Neurodevelopmental Disorders"
S20	DE "Tourette Syndrome"
S19	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18	TI (((s#nc#ron* OR de-s#nc#ron* OR des#nc#ron*) N2 (cortex OR cortical OR cortices))) OR AB (((s#nc#ron* OR de-s#nc#ron* OR des#nc#ron*) N2 (cortex OR cortical OR cortices))) OR SU (((s#nc#ron* OR de-s#nc#ron* OR des#nc#ron*) N2 (cortex OR cortical OR cortices)))
S17	TI (((feedback# N0 psyc#olog*) OR (feed-back N0 psyc#olog*))) OR AB (((feedback# N0 psyc#olog*) OR (feed-back N0 psyc#olog*))) OR SU (((feedback# N0 psyc#olog*) OR (feed-back N0 psyc#olog*)))
S16	DE "Feedback"
S15	TI ((((feedback# OR (feed W0 back*) OR biofeedback# OR (bio W0 feedback#) OR (biofeed W0 back) OR (bio W0 feed W0 back)) N2 (bogus OR false OR psyc#oph#siolog* OR (psyc#o W0 ph#siolog*) OR psyc#olog*)) OR m#ofeedback* OR (m#o W0 feedback*) OR (m#ofeed W0 back) OR (m#o W0 feed W0 back))) OR AB ((((feedback# OR (feed W0 back*) OR biofeedback# OR (bio W0 feedback#) OR (biofeed W0 back) OR (bio W0 feed W0 back)) N2 (bogus OR false OR psyc#oph#siolog* OR (psyc#o W0 ph#siolog*) OR psyc#olog*)) OR m#ofeedback* OR (m#o W0 feedback*) OR (m#ofeed W0 back) OR (m#o W0 feed W0 back))) OR SU ((((feedback# OR (feed W0 back*) OR biofeedback# OR (bio W0 feedback#) OR (biofeed W0 back) OR (bio W0 feed W0 back)) N2 (bogus OR false OR psyc#oph#siolog* OR (psyc#o W0 ph#siolog*) OR psyc#olog*)) OR m#ofeedback* OR (m#o W0 feedback*) OR (m#ofeed W0 back) OR (m#o W0 feed W0 back)))
S14	DE "Biofeedback Training"
S13	DE "Biofeedback"
S12	TI (((rhythm# N2 (alpha OR alfa OR bet#a OR delta OR gam#a OR t#eta OR mu)) OR brainwave# OR (brain W0 wave#))) OR AB (((rhythm# N2 (alpha OR alfa OR bet#a OR delta OR gam#a OR t#eta OR mu)) OR brainwave# OR (brain W0 wave#))) OR SU (((rhythm# N2 (alpha OR alfa OR bet#a OR delta OR gam#a OR t#eta OR mu)) OR brainwave# OR (brain W0 wave#)))
S11	DE "Theta Rhythm"

S10	DE "Gamma Rhythm"
S9	DE "Delta Rhythm"
S8	DE "Beta Rhythm"
S7	DE "Alpha Rhythm"
S6	TI ((eeg# OR electroencephalogra* OR (electro W0 encephalogra*) OR (electrical N0 activit*))) OR AB ((eeg# OR electroencephalogra* OR (electro W0 encephalogra*) OR (electrical N0 activit*))) OR SU ((eeg# OR electroencephalogra* OR (electro W0 encephalogra*) OR (electrical N0 activit*)))
S5	DE "Electrical Activity"
S4	DE "Electroencephalography"
S3	TI ((((alpha OR brainwave# OR (brain W0 wave#) OR electrom#ogra* OR (electro W0 m#ogra*) OR electroencephalogr* OR (electro W0 encephalogr*)) N2 (feedback# OR (feed W0 back#) OR biofeedback# OR (bio W0 feedback#))) OR neurofeedback# OR (neuro W0 feedback#) OR (neurofeed W0 back) OR (neuro W0 feed W0 back) OR neurobiofeedback OR neuro-biofeedback OR neurotherap* OR neuro-therap* OR neurorehabilit* OR neuro-rehabilit*)) OR AB ((((alpha OR brainwave# OR (brain W0 wave#) OR electrom#ogra* OR (electro W0 m#ogra*) OR electroencephalogr* OR (electro W0 encephalogr*)) N2 (feedback# OR (feed W0 back#) OR biofeedback# OR (bio W0 feedback#))) OR neurofeedback# OR (neuro W0 feedback#) OR (neurofeed W0 back) OR (neuro W0 feed W0 back) OR neurobiofeedback OR neuro-biofeedback OR neurotherap* OR neuro-therap* OR neurorehabilit* OR neuro-rehabilit*)) OR SU ((((alpha OR brainwave# OR (brain W0 wave#) OR electrom#ogra* OR (electro W0 m#ogra*) OR electroencephalogr* OR (electro W0 encephalogr*)) N2 (feedback# OR (feed W0 back#) OR biofeedback# OR (bio W0 feedback#))) OR neurofeedback# OR (neuro W0 feedback#) OR (neurofeed W0 back) OR (neuro W0 feed W0 back) OR neurobiofeedback OR neuro-biofeedback OR neurotherap* OR neuro-therap* OR neurorehabilit* OR neuro-rehabilit* OR (neurolog* W0 rehabilit*)))
S2	DE "Neurorehabilitation"
S1	DE "Neurotherapy"

Table 4: Search strategy using APA PsycINFO database

D. Yale Global Tic Severity Scale (YGTSS)

ID #:❑❑❑❑

Y G T S S

Yale Global Tic Severity Scale

Yale Child Study Center

Figur

Reprinted by permission of the author, James Leckman, M.D. *October 1992 version*

YALE GLOBAL TIC SEVERITY SCALE

NAME: TODAY'S DATE : / /

RATER:

MOTOR TIC SYMPTOM CHECKLIST (Check motor tics present during **past week** and **worst ever period** .)

	CURRENT	WORST EVER
•**Simple Motor Tics** (Rapid, Darting, "Meaningless"):		
❑	Eye blinking	Eye blinking
❑	Eye movements	Eye movements
❑	Nose movements	Nose movements
❑	Mouth movements	Mouth movements
❑	Facial grimace	Facial grimace
❑	Head jerks/movements	Head jerks/movements
❑	Shoulder shrugs	Shoulder shrugs
❑	Arm movements	Arm movements
❑	Hand movements	Hand movements
❑	Abdominal tensing	Abdominal tensing
❑	Leg, foot, or toe movements	Leg, foot, or toe movements
❑	Other (describe):	Other (describe):
•**Complex Motor Tics** (Slower, "Purposeful"):		
❑	Eye movements	Eye movements
❑	Mouth movements	Mouth movements
❑	Facial movements or expressions	Facial movements or expressions
❑	Head gestures or movements	Head gestures or movements
❑	Shoulder movements	Shoulder movements
❑	Arm movements	Arm movements
❑	Hand movements	Hand movements
❑	Writing tics	Writing tics
❑	Dystonic postures	Dystonic postures
❑	Bending or gyrating	Bending or gyrating
❑	Rotating	Rotating
❑	Leg or foot or toe movements	Leg or foot or toe movements
❑	Blocking	Blocking
❑	Tic related compulsive behaviors (touching, tapping, grooming, evening-up)	Tic related compulsive behaviors (touching, tapping, grooming, evening-up)
❑	Copropraxia	Copropraxia
❑	Self-abusive behavior	Self-abusive behavior
❑	Paroxysms of tics (displays), duration ___ seconds	Paroxysms of tics (displays), duration ___ seconds
❑	Disinhibited behavior (describe):*	Disinhibited behavior (describe):*
❑	Other (describe):	Other (describe):

PHONIC TIC SYMPTOM CHECKLIST (Check phonic tics for **past week** and **worst ever period.**)

CURRENT	WORST EVER
•**Simple Phonic Symptoms** (Fast, "Meaningless" Sounds):	
❑ Sounds, noises (circle: coughing, throat clearing, sniffing, or animal or bird noises)	❑ Sounds, noises (circle: coughing, throat clearing, sniffing, or animal or bird noises)
❑ Other (list): _____	❑ Other (list): _____
•**Complex Phonic Symptoms** (Words, Phrases, Statements):	
❑ Syllables (list) _____	❑ Syllables (list) _____
❑ Words (list) _____	❑ Words (list) _____
❑ Coprolalia (list) _____	❑ Coprolalia (list) _____
❑ Echolalia	❑ Echolalia
❑ Palalalia	❑ Palalalia
❑ Blocking	❑ Blocking
❑ Speech atypicalities (describe) _____	❑ Speech atypicalities (describe) _____
❑ Disinhibited speech (describe)* _____	❑Disinhibited speech (describe)* _____

* Do not include disinhibitions in ratings of tic behaviors

NUMBER	Current Motor	Current Phonic	Worst Ever Motor	Worst Ever Phonic
None	0	0	0	0
Single tic	1	1	1	1
Multiple discrete tics (2-5)	2	2	2	2
Multiple discrete tics (>5)	3	3	3	3
Multiple discrete tics plus as least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics	4	4	4	4
Multiple discrete tics plus several (>2) orchestrated paroxysms of multiple simultaneous or sequential tics that where it is difficult to distinguish discrete tics	5	5	5	5

FREQUENCY	Motor	Phonic	Motor	Phonic
NONE No evidence of specific tic behaviors	0	0	0	0
RARELY Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.	1	1	1	1
OCCASIONALLY Specific tic behaviors are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.	2	2	2	2
FREQUENTLY Specific tic behaviors are present on a daily basis. Tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.	3	3	3	3
ALMOST ALWAYS Specific tic behaviors are present virtually every waking hour of every day, and periods of sustained tic behaviors occur regularly. Bouts of tics are common and are not limited to a single setting.	4	4	4	4
ALWAYS Specific tic behaviors are present virtually all the time. Tic free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.	5	5	5	5

INTENSITY

	Current		Worst Ever	
	Motor	Phonic	Motor	Phonic
ABSENT	0	0	0	0
MINIMAL INTENSITY Tics not visible or audible (based solely on patient's private experience) or tics are less forceful than comparable voluntary actions and are typically not noticed because of their intensity.	1	1	1	1
MILD INTENSITY Tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.	2	2	2	2
MODERATE INTENSITY Tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character.	3	3	3	3
MARKED INTENSITY Tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character. Such tics frequently call attention to the individual because of their forceful and exaggerated character.	4	4	4	4
SEVERE INTENSITY Tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.	5	5	5	5

COMPLEXITY

	Motor	Phonic	Motor	Phonic
NONE If present, all tics are clearly "simple" (sudden, brief, purposeless) in character.	0	0	0	0
BORDERLINE Some tics are not clearly "simple" in character.	1	1	1	1
MILD Some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviors, such as grooming, syllables, or brief meaningful utterances such as "ah huh," "hi" that could be readily camouflaged.	2	2	2	2
MODERATE Some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behavior or speech (picking, tapping, saying "you bet" or "honey", brief echolalia).	3	3	3	3
MARKED Some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre or obscene character (a lengthy facial contortion, touching genitals, echolalia, speech atypicalities, longer bouts of saying "what do you mean" repeatedly, or saying "fu" or "sh").	4	4	4	4
SEVERE Some tics involve lengthy bouts of orchestrated behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre or obscene character (lengthy displays or utterances often involving copropraxia, self-abusive behavior, or coprolalia).	5	5	5	5

INTERFERENCE

	Motor	Phonic	Moter	Phonic
NONE	0	0	0	0
MINIMAL When tics are present, they do not interrupt the flow of behavior or speech.	1	1	1	1
MILD When tics are present, they occasionally interrupt the flow of behavior or speech.	2	2	2	2
MODERATE When tics are present, they frequently interrupt the flow of behavior or speech.	3	3	3	3
MARKED When tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt intended action or communication.	4	4	4	4
SEVERE When tics are present, they frequently disrupt intended action or communication.	5	5	5	5

IMPAIRMENT	Current	Worst ever
NONE	0	0
MINIMAL Tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics vis a vis the future, periodic, slight increase in family tensions because of tics, friends or acquaintances may occasionally notice or comment about tics in an upsetting way).	10	10
MILD Tics associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning.	20	20
MODERATE Tics associated with some clear problems in self-esteem family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school or job performance because of tics).	30	30
MARKED Tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.	40	40
SEVERE Tics associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (severe depression with suicidal ideation, disruption of the family (separation/divorce, residential placement), disruption of social tics - severely restricted life because of social stigma and social avoidance, removal from school or loss of job).	50	50

E. JBI Critical Appraisal Checklist for Case Reports

JBI Critical Appraisal Checklist for Case Reports

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	☐	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	☐	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	☐	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	☐	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	☐	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	☐	☐	☐
8. Does the case report provide takeaway lessons?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Figure 3: JBI critical appraisal checklist for case reports

F. Cochrane Collaboration's Tool for Assessing the Risk of Bias

Appendix F. Cochrane Risk of Bias Tool

Use the modified Cochrane Collaboration tool to assess risk of bias for randomized controlled trials. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).

AUB KQ1 Risk of Bias Assessment (Reference ID #)

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Selection bias ***Random sequence generation***	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**High** **Low** **Unclear**	
Selection bias ***Allocation concealment***	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	**High** **Low** **Unclear**	
Reporting bias ***Selective reporting***	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment†	**High** **Low** **Unclear**	
Other bias ***Other sources of bias***	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	**High** **Low** **Unclear**	

* If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry.
† It is likely that the majority of studies will fall into this category.

Assess each main or class of outcomes for each of the following. Indicate the specific outcome.

AUB KQ1 Risk of Bias Assessment (Reference ID #)

Outcome:

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	**High** **Low** **Unclear**	

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