European Review for Medical and Pharmacological Sciences 2022; 26: 6856-6870

Non-pharmacologic approaches to neurological stimulation in patients with severe brain injuries: a systematic review

L. DI SARNO, A. CURATOLA, I. CAMMISA, L. CAPOSSELA, G. EFTIMIADI, A. GATTO, A. CHIARETTI

Department of Pediatrics, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Abstract. – OBJECTIVE: This review aimed to evaluate and summarize the current knowledge about the non-pharmacological neurological stimulation (NPNS) in patients with severe brain injuries (SBI). The approaches we analyzed included sensory stimulation, music therapy, virtual reality, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS).

MATERIALS AND METHODS: We performed a review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards. The key words used for the search across electronic databases such as PubMed and the Cochrane Library were "brain injury" or "coma" or "vegetative state" and "neurological stimulation" or "sensory stimulation" or "music therapy" or "virtual reality" or "transcranial direct current stimulation" or "transcranial magnetic stimulation".

RESULTS: 38 studies matched the inclusion criteria. These articles were categorized into five clusters: sensory stimulation, music therapy, virtual reality, transcranial direct current stimulation and transcranial magnetic stimulation. Hence, a concise summary of each study was made up, including study population characteristics, type of non-pharmacological neurological stimulation, neurological clinical outcomes or neuroimaging outcomes.

CONCLUSIONS: Overall, all the non-pharmacological approaches to neurological stimulation in patients with SBI seem to be innovative and promising. Further randomized clinical trials, including a wide range of patients, will be necessary to definitely validate these methods and develop standardized protocols shared in the scientific community.

Key Words:

Brain injury, Neurological stimulation, Music therapy, Virtual reality, Transcranial direct current stimulation, Transcranial magnetic stimulation.

Abbreviations

Non-pharmacological neurological stimulation (NPNS); Severe brain injuries (SBI); Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); Glasgow Coma Scale (GCS); Coma recovery scale- revised (CRS-R); Magnetic Resonance Imaging (MRI); Voxel-based morphometry (VBM); Electroencephalography (EEG); Institutes for the Achievement of Human Potential (IAHP); Sensory stimulation (SS); Randomized controlled trial (RCT); Familiar auditory sensory training (FAST); Intelligence Quotient (IQ); Melodic Intonation Therapy (MIT); Rhythmic auditory stimulation (RAS); Patterned sensory enhancement (PSE); Virtual reality (VR); Virtual reality driving simulation rehabilitation training (VRDS-RT); Paced Auditory Serial Addition Task (PASAT); Gait Real-time Analysis Interactive Lab (GRAIL); Transcranial direct current stimulation (tDCS); Transcranial magnetic stimulation (TMS); Traumatic brain injury (TBI); Unresponsive wakefulness syndrome (UWS).

Introduction

Neurological disorders, a widespread series of conditions caused by injury or disease of the nervous system, concern up to 1 billion people all around the world and include 6.3% of pathologies[1]. These clinical conditions involve motor and sensory issues but impact cognitive and behavioral skills as well, which require complex long-term multitasking rehabilitation programs. Neurorehabilitation is a set of complex multidisciplinary interventions, both pharmacological and non-pharmacological, aimed to assist patients with neurological injury, promote recovery and reduce disability[1]. The developments of technology are providing newer and non-invasive alternative approaches with a great potential above all in children, in which the relative neuro-plasticity offers a larger window of opportunity for intervention[2]. Neuro-plasticity is defined as the ability of synapses to increase or decrease their activity, through mechanisms of long-term potentiation and long-term depression[1]. The children's immature brain, however, is a dynamic environment with significant chang-

Corresponding Author: Lorenzo Di Sarno, MD; e-mail: lorenzodisarno1993@gmail.com

es to cellular composition, neural circuitry and blood flow occurring throughout childhood[3]. These variations affect the susceptibility of the child's brain to damage. In fact, if on the one hand it is known that younger brains naturally recover better than older brains, on the other various studies suggested that a young brain is more susceptible to injury[4,5]. It also has been suggested that a brain insult during a critical period of growth can eventually lead to cessation of development[6]. Neurological stimulation is a safe, low-invasive, non-pharmacologic neuro-rehabilitative approach based on the exposure to repetitive, frequent and moderate-to-high intensity stimuli (visual, auditory, tactile, olfactory, gustatory, and proprioceptive). It is applied in unimodal or multimodal programs, in order to facilitate the recovery process and prevent sensory deprivation in neurological disorders[2].

The main aim of this review was to evaluate and summarize the current knowledge about the non-pharmacological neurological stimulation (NPNS) in patients with severe brain injuries (SBI).

Materials and Methods

We examined the following bibliographic electronic databases: PubMed and the Cochrane Library, from inception date until February 2022. The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[7] and was limited to English-language papers that focused on NPNS in patients with SBI. To be considered eligible for the review, papers had to include the following components: (1) subjects (adults and children) with diagnosis of SBI; (2) who received NPNS as treatment; (3) neurological clinical outcomes evaluated by assessment scales – Glasgow Coma Scale (GCS), Coma recovery scale- revised (CRS-R), etc. – or by radiological examinations or by Electroencephalography (EEG). We excluded: non-English language papers and studies in which neurological outcomes were not expressed in assessment scales or evaluated by radiological examinations or EEG. The key words used for the search across electronic databases were: "brain injury" or "coma" or "vegetative state" and "neurological stimulation" or "sensory stimulation" or "music therapy" or "virtual reality" or "transcranial direct current stimulation" or "transcranial magnetic stimulation". The abstracts of the papers were assessed by a single reviewer (LDS) who strictly applied the inclusion/exclusion criteria mentioned above to decide whether a paper was eligible for full review. Each paper that met the eligibility criteria was reviewed and analyzed in full text by two authors (LDS and AC) and any discrepancies among them were solved by debate. Due to the heterogeneity of the articles examined, we focused on a qualitative analysis.

Data Extraction and Ethics Statements

The data extracted from each eligible paper included: study population characteristics, type of NPNS, neurological clinical outcomes and neuroimaging outcomes. In this review, we analyzed the current literature on severe brain injury and neurorehabilitation techniques. Thus, ethical approval was not required.

Results

Overall, we identified 453 records through database searching. As first step, we excluded 38 articles in non-English language, 2 records whose related articles were not available, 2 articles concerning ongoing trials and 195 duplicated papers. As second step, we eliminated 176 records by evaluating only title and abstract because they did not match the inclusive criteria we mentioned before. Of the remaining 40 studies, we excluded 2 through a further discussion among authors upon the reliability of data. Thus, 38 selected articles were included in the review. The detailed selection of the literature is showed in Figure 1. The characteristics of all included studies are summarised in Table I.

Sensory Stimulation

Firstly, based on animal research, Rosenzweig et al[8] demonstrated in a pioneering study that an "environmental enrichment" induces changes in cortical thickness and in neuron size. Exposure to an enriched environment after experimental brain lesions has shown to be positive in terms of recovery of cognitive and motor functions[9]. The Institutes for the Achievement of Human Potential (IAHP) have introduced sensory stimulation (SS) in the field of neurorehabilitation[10]. The SS can be active, with the participation of patients, or passive with no required attention. The latter is useful in patients with disorders of consciousness because of altered vigilance levels[10]. An early application, within three months from brain injury, is preferred even if most recent data are assessing

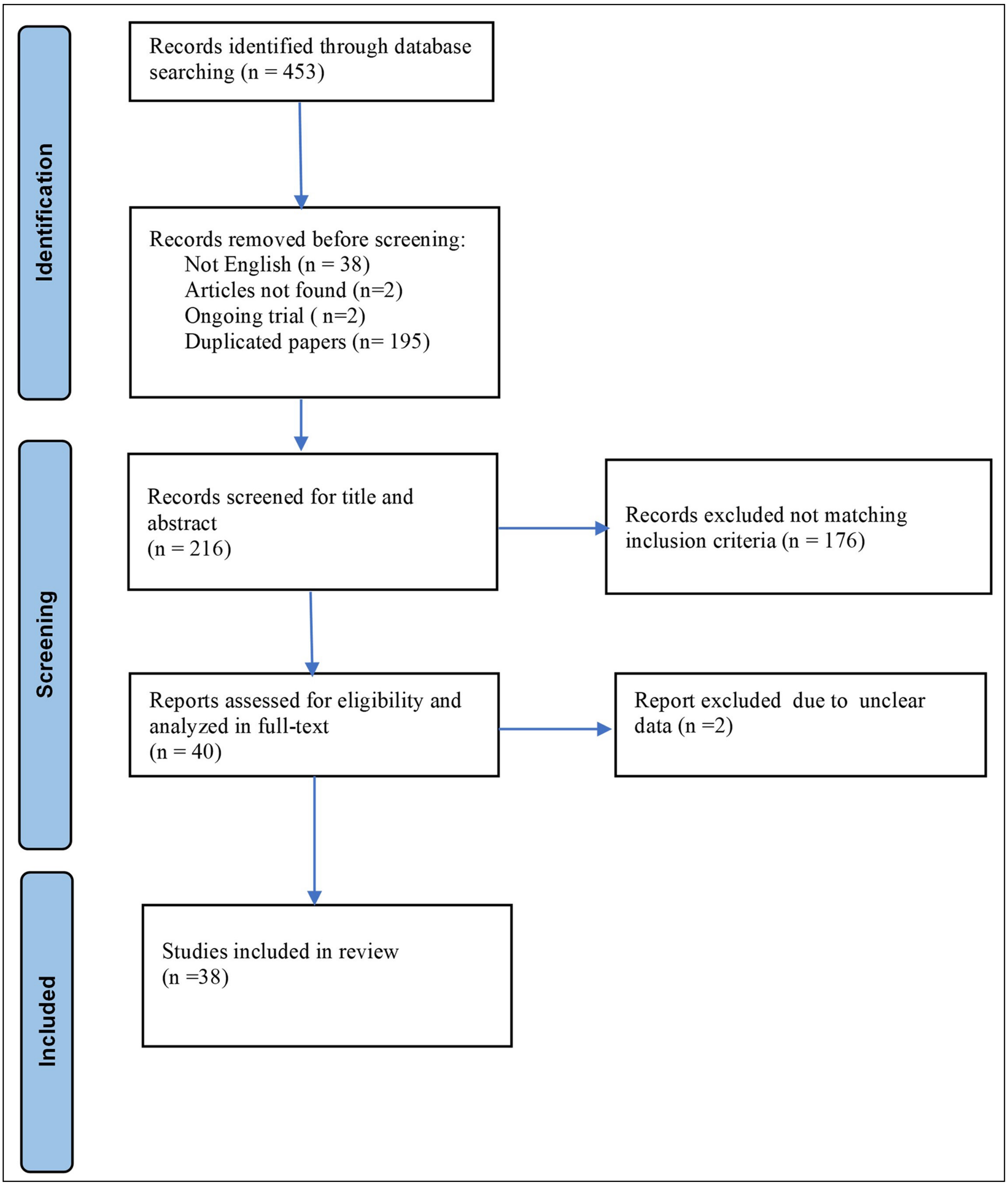

Figure 1. Flow diagram of this study selection[7].

a potential for recovery also years after the initial injury[11]. Mitchell et al[12] in a study including 12 patients with SBI subjected to five sensory stimuli applied for 1 months, showed an increase of GCS and a decrease of coma duration.-

Mackay et al[13] found that in patients with SBI the length of hospitalization for coma and rehabilitation was about one third in patients that received acute care services at hospitals with a formalized early intervention program, including SS. Also, Wood et al[14], in a controlled pilot study, stated that patients treated with regulated SS showed a shorter hospitalization and better outcome.

In 2002, Lombardi et al[15] in a systematic review stated that there was no consistent evidence to rule out the efficacy of multisensory programs in patients in coma or vegetative state. Oh et al[16] in

Table I. The characteristics of all included studies.

Study	Sample type	Sample size	Study design	Type of Stimulation	Assessment tool	Neurological Outcomes	Outcomes assessed by Neuroimaging or EEG
Mitchell et al[12] (1990)	Acquired SHI	24	Clinical trial	Multi-sensory stimulation	GCS	Higher weekly GCS scores (14 *vs.* 13.08 after 4 weeks) and shorter coma duration (22 days *vs.* 26.9 days).	
Mackay et al[13] (1992)	SHI	38	Comparative study	Acute care services with/without formalized traumatic brain injury programs.	RLA	Reduced coma length (18.9 *vs.* 53.8 days) and higher cognitive levels at discharge (RLA 5.6 *vs.* 4.0)	
Wood et al[14] (1992)	Comatose patients for at least 28 days following a closed-head, acceleration-deceleration injury	8	Controlled pilot study	SS	GCS RLA	Shorter hospitalization (88.7 *vs.* 125.7 days) and better GCS (from 9-10 to 14-15 *vs.* from 9-10 to 10-12) and RLA (4/3 point gain VS no gains).	
Oh et al[16] (2003)	Comatose patients with recent TBI	7	Clinical trial	Multi-sensory stimulation	GCS	Increased GCS (to a maximum of 10-13) after first and second period of intervention. GCS decreased after 2 weeks, while the second one registered a lasting effect on consciousness level.	
Lotze et al[17] (2011)	Patients in persistent vegetative state or minimally conscious state	7	ABA-BAB design study	SS	A 10-cm visual analogue scale	A long-term SS therapy (mean scores 2.46 ± 0.44 at the beginning and 3.51 ± 0.45 at the end of treatment) and social-tactile intervention for STI (1.94c± 0.35 at the beginning and 3.09 ± 0.53 at the end of treatment) causes behavioural changes	
Di Stefano et al[19] (2012)	Vegetative state or minimally conscious state for at least 3 months after brain injury.	12	Clinical trial	Multi-sensory stimulation	WHIM	Higher and better behaviour during effective/emotional stimulation.	
Tavangar et al[20] (2015)	SBI with acute subdural hematoma	40	Single-blind RCT	Music Therapy	GCS	Mean GCS from the fourth day of stimulation 7.75 *vs.* 10.25 on the 10th day of intervention	
Pape et al[21] (2015)	DOC for at least 28 days and within 1 year of TBI. CNC	15	Double-blind RCT	FAST protocol	DOCS CNC	Mean DOCS change was not different; improvement of CNC (1.01 *vs.* 0.25).	fMRI: increased whole brain activation, above all in language regions
Salmani et al[23] (2017)	Severe TBI and GCS 5-8.	90	RCT	SS by family members or a non-familiar trained person.	GCS CRS-R	Improved GCS and CRS score in the family intervention group compared to placebo (a trained nurse) and control group	
Moattari et al[22] (2016)	SHI comatose patients with a GCS 3 – 8 and a RLA I – II.	60	Double-blind randomized clinical trial	Multi-sensory stimulation	GCS RLA WNSSP	Higher GCS, RLA and WNSSP in patients who received stimulation from their family members compared to a placebo (a trained nurse) or to control group	
Cheng et al[10] (2018)	SBI patients diagnosed as being in a vegetative state or in a minimally conscious state.	29	Clinical study	Multi-sensory stimulation	CRS-R	Higher scores for the oromotor subscale (1.33 VS 1.18) and the arousal subscale (1.91 VS 1.82) in minimally conscious state patients.	fMRI: higher activation in the right middle frontal gyrus, right superior temporal gyrus and bilateral ventro-anterior thalamic nucleus.
Pape et al[24] (2020)	DOC for at least 28 days in patients with severe TBI.	16	Pilot study	FAST protocol	DOCS-25 CNC	Three out of the four FAST participants and all four of the placebo participants made meaningful DOCS-25 Auditory-Language gains.	fMRI: higher activation of the left and right inferior longitudinal fasciculus and right superior frontal-occipital fasciculus
Hotz et al[25] (2006)	SBI and anoxic event	15	Observational study	Multi-sensory stimulation	GCS MAS RLA ABS FIM	Improvement in functional and cognitive outcome (RLAS and FIM); a reduction of muscle tone in all the affected spastic limbs measured (MAS)	

Continued

Table I *(Continued)*. The characteristics of all included studies.

Study	Sample type	Sample size	Study design	Type of Stimulation	Assessment tool	Neurological Outcomes	Outcomes assessed by Neuroimaging or EEG
Wu et al[31] (2018)	UWS and MCS	28	Case-control study	Music Therapy	CRS-R	CRS-R score was higher in the MCS compared to the UWS group (9.43 ± 2.37 *vs.* 5.14 ± 1.68).	EEG: increased brain activity
Sarkamo et al[32] (2008)	Middle cerebral artery stroke	60	Single-Blind RCT	Music therapy	RBMT WMS BDAE Stroop subtests	At the 6-month stage, verbal memory recovery and focused attention recovery was significantly better in the music group than in the language group	
Ineke van der Meulen et al[34] (2014)	Non-fluent aphasia after left hemisphere stroke	27	Multicenter RCT	MIT	Sabadel story retelling task ANELT AAT MIT repetition task SAT	Significant improvement on all outcomes measures except for the Sabadel	
Raglio et al[35] (2016)	Aphasic patients with previous stroke	20	RCT	Music therapy	AAT Token Test Boston naming Test Short Form Health SF36	Improvement in AAT and SF36 scores when music-therapy was associated to speech and language therapy	
Thaut et al[38] (2007)	Stroke patients with mild-moderate sensory dysfunction and lower limb spasticity.	78	Single-blind, RCT	RAS training protocol	Functional Gait Improvement	Improved velocity (164% VS 107%), stride length (88% VS 34%), cadence (56% VS 45%) and symmetry (32% VS 16%) of gait.	
Altemuller et al[39] (2009)	moderate impairment of motor function of the upper extremities after stroke.	32	RCT	Music therapy	ARAT Arm Paresis Score BBT 9HPT	Improvement of movement range, speed and quality. ARAT from 33.3 to 41.4; Arm Paresis Score from 4.5 to 5.9; BBT from 25.12 to 35.1; 9HPT from 4.1 to 5.4.	
Kim et al[40] (2012)	Subacute hemiplegic patients	20	Clinical study	RAS training protocol	ABC DGI FSST FAC TUG	Better response in all selected score comparing pre-test and post-test value: ABC scale from 42.46 to 54.98; DGI from 11.22 to 20.67; FSST from 26.42 to 16.68; FAC from 3 to 4.3; TUG from 20.25 to 13.53.	
Suh et al[41] (2014)	Hemiplegic stroke patients	16	RCT	RAS training	Functional Gait Improvement	Improvement in RAS group for overall stability index ($p = 0.043$), mediolateral index ($p = 0.006$), anteroposterior index ($p = 0.016$), gait velocity ($p = 0.012$), stride length ($p = 0.03$) and cadence ($p = 0.012$) over the control group	
Christiansen et al[46] (1998)	SHI	30	Clinical study	VR	VR Score for each item	The mean assessment total score for the first test was 156.37 (SD = 14.33), and the mean total for the retest was 161.00 (SD = 13.02).	
Cox et al[47] (2010)	SHI	11	RCT	VRDSRT	Road Rage Questionnaire CARDS	Better driving performance and decreased road rage and risky driving (CARDS 11.2 *vs.* 22.3)	
Gamito et al[48] (2011)	TBI.	1	Clinical trial	VR platform	PASAT	Improvement in working memory and attention levels.	

Continued

Table I *(Continued)*. The characteristics of all included studies.

Study	Sample type	Sample size	Study design	Type of Stimulation	Assessment tool	Neurological Outcomes	Outcomes assessed by Neuroimaging or EEG
Biffi et al[49] (2017)	TBI	12	Clinical trial	GRAIL, an instrumented multi-sensor platform based on immersive VR	GMFM FAQ 6minWT OGA GGA	Improvement of Gross Motor abilities; decrease of the Gillette Gait Index for the impaired side and a general increase of symmetry; improvements in spatiotemporal parameters and joints range of motion	
Choi et al[50] (2021)	TBI	80	Multicentre, single-blind RCT	VR	MA-2 Upper Limb Physician's Rating Scale Pediatric Evaluation of Disability; Inventory Computer Adaptive Test	Upgrade of upper-limb skill functions (MA-2 10.09 VS 3.65)	
Keller et al[51] (2020)	TBI and upper limb paresis	35	Prospective cohort study	VAI	ARAT Modified Ashworth Scale	Higher improvement of impairment of affected upper extremity	Voxel-based morphometry: volumetric increase of grey matter in five brain areas
Kang et al[56] (2012)	TBI with attention deficit	9	Double-blind, crossover design	20 minutes of anodal tDCS (2 mA)	Computerized contrast reaction time Superlab pro v.4.0 software	The intervention group showed a short-lasting reduced reaction time in accomplishing a certain computerized task compared to baseline	
Lésniak et al[57] (2014)	TBI	23	Randomized-controlled trial	anodal tDCS (1 mA for 10 minutes), along with the subsequent rehabilitative cognitive training for 15 day	RAVLT PRM PASAT SSP RVP EIBQ	No substantial differences in outcome scores	
Middleton et al[58] (2014)	TBI	5	Open label	24 sessions of bihemispheric tDCS (1.5 mA for 15 min)	UE Fugl-Meyer Purdue Pegboard Box and Block Stroke Impact Scale Robotic measures	Motor function improved	
Sacco et al[59] (2016)	TBI	32	Randomized-controlled trial	a session of 20 minutes of tDCS, twice a day for 5 consecutive days	Computer-assisted cognitive training on Divided Attention	The intervention group considerably enhanced performance after treatment	fMRI in the intervention group showed lower cerebral activations after sessions in the right superior temporal gyrus, right and left middle frontal gyrus, right postcentral gyrus and left inferior frontal gyrus.
Naro et al[62] (2014)	UWS in post anoxic condition	10	Clinical study	High-frequency rTMS in the dorsolateral prefrontal cortex	CRS-R	Increased CRS-R scoring, from 2 to 3 points, in 3 patients with a short effect	

Continued

Table I ***(Continued).*** The characteristics of all included studies.

Study	Sample type	Sample size	Study design	Type of Stimulation	Assessment tool	Neurological Outcomes	Outcomes assessed by Neuroimaging or EEG
He et al[63] (2018)	VS, MCS and EMCS	6	Randomized-controlled trial	rTMS in the primary motor cortex	CRS-R	Increased CRS-R total score (from 6 to 8) and CRS-R motor score (from 1 to 3) in one patient	EEG: in one patient great reactivity of brain in response to real rTMS especially at the F3 and C3 electrodes,
Wu et al[65] (2018)	UWS or MCS	8	Clinical study	Theta burst stimulation	CRS-R	CRS-R score improved from a mean value of 6.0±1.0 to 9.9±2.2 at T1 and to 8.9±2.3 at T2.	EEG: changes in spontaneous EEG activity with more power in the alpha band at both T1 and T2
Liu et al[64] (2018)	DOC due to traumatic, anoxic and hemorrhagic injury	7	Randomized, sham-controlled study	High-Frequency rTMS	CRS-R	CRS-R total score increased from 15 to 23 points in one patient	fMRI: in one patient functional connectivity was increased
Xia et al[66] (2017)	MCS and VS	16	Prospective single-blinded study	High-frequency rTMS on the left dorsolateral prefrontal cortex	CRS-R CGI-I	The CRS-R scores were increased in all 5 MCS patients and in 4 out of 11 VS patients.	
Kirton et al[67] (2008)	Subcortical arterial ischemic stroke	10	Randomized Controlled Trial	Low frequency rTMS	MAUEF	At day 10, MAUEF total scores had improved in rTMS-treated patients.	
Kirton et al[68] (2016)	Hemiparetic children with MRI-confirmed perinatal stroke	45	Randomized Controlled Trial	rTMS and CIMT	AHA COPM	AHA: rTMS + CIMT group improved by 5.91 units compared to 0.62 units in those receiving neither. COPM: rTMS was associated with significant gains in satisfaction and performance	

EEG: electroencephalogram; SHI: Severe Head Injury; SS: Sensory Stimulation; RLA: Rancho Los Amigos scale; GCS: Glasgow coma scale; WHIM: The Wessex Head Injury Matrix; SBI: severe brain injury; RCT: randomized Clinical Trial; TBI: Traumatic Brain Injury; DOCS: Disorders of Consciousness Scale; CNC:Coma Near Coma; DOC: Disordered consciousness; FAST: Familiar Auditory Sensory Training; MRI: Magnetic resonance imaging; CRS-R: Coma Recovery Scale-Revised; WNSSP: Western Neuro-Sensory stimulation profile; MAS: Modified Ashworth Scale (MAS); ABS: Agitated Behaviour Scale; FIM: Functional Independent;Measure; UWS: unresponsive wakefulness syndrome; MCS: minimally conscious state; RBMT: Rivermead Behavioural Memory Test; WMS: Wechsler Memory Scale-Revised; BDAE: Boston Diagnostic Aphasia Examination; MIT: Melodic Intonation Therapy; ANELT: Amsterdam Nijmegen Everyday Language Test; SAT: Semantic Association Task; AAT: Aachener Aphasie Test; RAS: rythmic auditory stimulation; Token Test; Boston naming Test; S F36: Short Form Health Survey 36; ARAT: Action Research Arm Test; BBT: Box and Block Test; 9HPT: Nine Hole Pegboard Test; ABC: Activities-specific Balance Confidence Scale; DGI: Dynamic Gait Index FSST: Four Square Step Test; FAC: Functional Ambulation Category; TUG: Timed Up and Go test; VR: Virtual Reality; VRDSRT: Virtual reality driving simulation rehabilitation training; CARDS: Cox Assessment of Risky Driving Scale; PASAT: Paced Auditory Serial Addition Task; GMFM: Gross Motor Function Measure; FAQ: Functional Assessment Questionnaire; 6minWT: 6-Minute Walk Test; OGA: 3D-Gait Analysis over ground; GGA: 3D-Gait Analysis on GRAIL; MA-2: Melbourne Assessment of Unilateral Upper Limb Function-2; VAI: Virtual anatomical interactivity; tDCS; Transcranial direct current stimulation; RAVLT: Rey's Auditory Verbal Learning Test; PRM: Pattern Recognition Memory test; SSP: Spatial Span ; RVP: Rapid Visual Information Processing; EIBQ: European injury brain questionnaire; TASIT: The Awareness of Social Inference Test; HVLT: Hopkins verbal learning test; BVMT: Brief Visual Memory; rTMS: Repetitive transcranial magnetic stimulation; VS: Vegetative state; EMCS: Emerged from MCS; CGI-I: Clinical Global Impression-Improvement scale; MAUEF: Melbourne assessment of upper extremity function; CIMT: Constraint-induced movement therapy; AHA: Assisting Hand Assessment; COPM: Canadian Occupational Performance Measure.

their study based on SS program in SBI patients, founded that after two interventions of stimulation, consciousness levels gradually increased and maintained a permanent duration. In 2011 Lotze et al[17] highlighted the chance of achieving behavioral changes in patients with minimally conscious state by long-term therapy with sensory stimulation and social-tactile intervention. In the following years of research, it seemed that autobiographical and emotional stimuli, could have a greater impact on neurological recovery[18]. Di Stefano et al[19] in a study evaluating patients with severe disorders of consciousness in the post-acute phase, recorded a better answer during the enriched stimulation compared to standard one. Following this assumption, Tavangar et al[20] in a RCT (randomized controlled trial) including comatose patients with SBI and acute subdural hematoma, showed an improvement of GCS scores from the fourth day in the intervention group. In 2015, Pape's studies introduced the familiar auditory sensory training (FAST) protocol, consisting of customized recordings of stories representing specific experiences told by people known to the patient. FAST protocol showed a clinical improvement and an activation in language regions using functional MRI[21]. Also Moattari et al[22] and Salmani et al[23], reported that patients receiving SS from their family members had better neurological outcomes than those who received it from other trained person. In 2018 Cheng et al[10] stated that SS improved behavioral responsiveness in minimally conscious state patients and, more exactly, increased arousal and oromotor functions. More recently, Pape et al[24] in a pilot study observed that SS treatment might have influenced functional and structural connectivity. Less is known about the application of SS in children with SBI. In 2005, Hotz et al[25] observed an improvement in cognitive outcome measures and a reduction of muscle tone in all affected spastic limbs. Subsequently, Eytan et al[26] developed a non-invasive model to monitor brain functions in critically ill children. They used a bedside functional imaging set-up planned to analyze cerebral activity by combining EEG recordings and multi-modal sensory stimulation[26].

Music Therapy

The first group to study the therapeutic effect of music on brain was Rauscher et al[27] in 1993: they founded that Intelligence Quotient (IQ) of college students improved after listening to the Mozart's sonata compared to a relaxation tape and silence. Against this, Chabris et al[28] in 1999, disproved the Mozart effect, stating that any cognitive enhancement was small and did not reflect any change in IQ. However, the role of music therapy for patients with acquired SBI has strengthened in the last few years. It represents a promising approach in the rehabilitation of movement, cognition, speech, emotions, and sensory perceptions[29]. Similarly to SS, music therapy aims to improve recovery by accelerating brain plasticity and avoiding sensory deprivation, acting on frontal, temporal, parietal, and subcortical networks[30]. Wu et al[31] showed a great activation of brain areas with white noise and music, compared to the baseline state, with a largest impact when the patient was called by his own name. Also, Sarkamo et al[32] documented an improvement of focused attention and verbal memory in patients with previous stroke who listened to their favorite music, compared to patients who listened to audio books or received no listening materials. It is also hypothesized that music influenced neural plasticity and brain repair by adjusting the secretion of steroid hormones[33]. Several music therapy protocols have been developed in the last few years regarding sensorimotor tasks, speech, language and cognitive training[30]. In a RCT Van der Meulen et al[34], analyzing the timing of Melodic Intonation Therapy (MIT), a language production treatment used for patients with aphasia, showed a significant impact of music sessions upon verbal communication and repetition. In 2016 Raglio et al[35] showed an improvement of spontaneous language and quality of life in patients with previous stroke treated with music therapy. The effects of music therapy do not concern only the cognitive sphere but also the executive one, with a key potential in the recovery of motor functions[36]. The benefit of music therapy in movements seems to be due to a functional neural connectivity among auditory cortex, executive control network and cerebellum[36]. Two kinds of interventions are mainly adopted in this field. The first one is Rhythmic auditory stimulation (RAS), consisting of therapeutic application of a pulsed rhythmic stimulation in order to improve gait related aspects of movement. The second one is Patterned sensory enhancement (PSE), consisting of application of rhythmic and harmonic musical elements with a focus on time and spatial orientation for non-rhythmic daily life movements[37]. In 2007 Thaut et al[38], comparing RAS and neurodevelopmental therapy for rehabilitation in stroke, founded that patients subjected to RAS registered an improvement in speed of walking. In 2009 Altenmuller et al[39], showed that a music-supported therapy program for motor functions improved movement range, speed and quality in stroke patients. Kim et al[40] in a study including subacute hemiplegic patients, showed how the conventional physical therapy integrated with RAS gave a better response. An improvement of gait velocity, stride length, cadence, and standing balance in hemiplegic stroke patients applying RAS was found also by Suh et al[41].

Virtual Reality

Current developments in technology are including virtual reality (VR) among rehabilitation activities. According to the Merriam-Webster Dictionary, VR is defined as "an artificial environment which is experienced through sensory stimuli (such as sights and sounds) provided by a computer and in which one's actions partially determine what happens in the environment"[42]. It can be classified, according to the level of isolation from the real world in: non-immersive (based on computer screen or tablet), semi-immersive (using large 3D screen) and fully-immersive (using a head-mounted display that allows interactions through multiple sensory channels)[43]. VR trainings, based on implicit learning, concrete tasks and focused attention, improve different aspects of function loss, above all execution capacity. VR creates illusory environments in which the sense of agency, defined as the experience of being the author of actions, is allowed by sensorimotor contingencies[43]. A meaningful and active interaction of patients with virtual world is needful to a complete immersion[44]. VR interventions offer several advantages. First of all, they offer a series of varied tasks, from sensory and motor to cognitive and socioemotional. Furthermore, in this modality patients are able to complete tasks directly at their home, decreasing imbalance regarding patients living in inland isolated areas. Lastly, young patients are more compliant using virtual platforms than applying traditional stimulation programs[45]. The first study stating that VR was acceptable for patients and a potential method for training and rehabilitation was conducted in 1998 by Christiansen et al[46]. In 2010, Cox et al[47] investigated the effectiveness of virtual reality driving simulation rehabilitation training (VRDSRT) in patients with SBI. In this study, the intervention group documented a better driving performance in addition to a decreased road rage and risky driving. In 2011, Gamito et al[48] used VR in a 20-years-old male with SBI, showing an improvement in working memory and attention levels, assessed by Paced Auditory Serial Addition Task (PASAT). In 2017, Biffi et al[49] used the GRAIL (Gait Real-time Analysis Interactive Lab), an instrumented multi-sensor platform based on immersive VR. They observed an improvement in standing and walking, a rise up of endurance and increased autonomy in daily life activities. More recently, Choi et al[50] in a RCT conducted on 80 children with cerebral palsy subjected to VR, observed an upgrade of upper-limb functions (unimanual dexterity, forearm articular movement, daily activities) in the intervention group. Also Keller et al[51], in a group of patients with SBI and upper limb paresis, subjected to VR, documented a volumetric increase of grey matter in the five following brain areas: the left hippocampal tail, the left caudate nucleus, the left rostral cingulate zone, the depth of the left central sulcus and the left visual cortex.

Transcranial Direct Current Stimulation (tDCS) And Transcranial Magnetic Stimulation (TMS)

Transcranial brain stimulation is based on electric or magnetic pulses delivered over the scalp. It is a growing field of neurorehabilitation for diagnosis, investigations and therapy of brain disorders[52]. A wide range of techniques has been applied over the years, with the development of non-invasive, well-tolerated and safe protocols[52]. The main non-invasive brain stimulations are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS)[52].

Transcranial direct current stimulation (tDCS) is a non-invasive cerebral stimulation method that acts by providing a direct current from a generator through electrodes placed on the scalp[53]. Thus, it causes an electric field that polarizes or depolarises neurons on the basis of the field's magnitude and direction[53]. These variations influence neuronal plasticity and cognitive functions as well. Conventionally, tDCS was thought to impact only on cortical areas but recent evidence show it can additionally involve subcortical and thalamo- cortical structures[54]. A constant flow of low intensity current (1-2 mA) is generated by an active electrode (anode or cathode) sited on a target brain area, while an electrode of opposite polarity is placed contralaterally[55]. Considering glutamatergic synapses, tDCS increases or reduces calcium inflow through NMDA receptors and voltage-gated calcium channels[55]. Because of new development of technologies, quite low cost and simplicity of use, there is increased interest in clinical applications of tDCS for treatment of severe SBI. In 2012 Kang et al[56] conducted a double blinded clinical trial on nine patients with attention deficit after traumatic brain injury. The intervention group was stimulated using real tDCS (2 mA for 20 minutes) on the left dorsolateral prefrontal cortex. The control group experienced a sham transcranial direct current stimulation (2 mA for 1 min) on the same cerebral area. Right after the stimulus, the intervention group showed a reduced reaction time in accomplishing a certain computerized task compared to baseline, while the sham stimulation group did not[56]. In 2014 Lesniak et al[57] conducted a randomized clinical trial. The participants were twenty-three adult patients with severe TBI (traumatic brain injury). The intervention group was exposed to anodal tDCS (about 1 mA for 10 minutes), along with the subsequent rehabilitative cognitive training for 15 days. Controls received anodal tDCS for 25 seconds with the same following treatment[57]. Three cognitive areas were tested, involving episodic memory, working memory and attention. Patients were tested before rehabilitation, after rehabilitation accomplishment and 4 months later. Results were similar before and after treatment in both groups[57]. In 2014 Middleton et al[58] focused on tDCS as an additional treatment to upper extremity rehabilitation for motor damages resulting from traumatic brain injury. Five patients accomplished 24 sessions consisting of physical therapy combined with bihemispheric tDCS. Outcomes assessed using Fugl-Meyer Assessment for upper extremity, Box and Block test, Stroke Impact Scale and robotic measures significatively enhanced after treatment. Increases recorded were confirmed six months later[58]. In 2016 Sacco et al[59] investigated the application of tDCS on the recovery of divided attention in patients with severe brain injury. Thirty-two patients were involved in this study. These patients were exposed to a session of 20 minutes of tDCS, twice a day for 5 consecutive days. The control group received sham tDCS. The intervention group considerably enhanced performance after treatment, with quicker reaction times and less omissions[59]. tDCS has also been tested as an option for a wide amount of different pediatric neurologic disorders[60]. Recent evidences[60] support minimal risk of severe adverse effects, such as seizure, hearing damage or pain in school-aged children[60]. The use of this technique has increasingly boosted in the last years but population samples remain modest if compared to adults. Due to the heterogeneity of stimulation protocols and lack of wider randomized clinical trials, more data on the efficacy and safety of tDCS in children are required to assess the impact on neurocognitive development[60].

TMS, used for the first time by Barker et al[61] in 1985, is based on the scientific principle of electromagnetic induction discovered by Faraday in 1831. It consists of brief, intense pulses of electric current delivered to a coil on the subject's head in order to produce a magnetic field that penetrates into the brain generating an electric current[61]. Various parameters influence the application of TMS: the position and type of coil (circular, double-cone, figure-of-eight) define the stimulated area and the features of the electric pulse set the cortical circuits to activate[52]. The single and paired-pulse protocols show temporary effects, whereas three or more pulses (known as repetitive pulse TMS or rTMS) bring about long-term changes in brain activity[52]. Although in the past TMS has been mainly used to map brain areas and record the motor evoked potentials, several studies have also investigated its neuromodulatory action leading to new treatment strategies for neurologic and psychiatric disorders[61]. In 2014, a study by Naro et al[62] in 10 subjects with unresponsive wakefulness syndrome (UWS) documented that a protocol of 10-Hz rTMS delivered over the dorsolateral prefrontal cortex improved the clinical features of 3 patients with a short-lasting effect. They also showed the absence of adverse effects after TMS[62]. In 2018, He et al[63] conducted a randomized sham-controlled trial in 6 patients with a diagnosis of Vegetative State, Minimally Conscious State or emerged from Minimally Conscious State. Only one patient showed long-lasting behavioral and neurophysiological modifications after real rTMS stimulation[63]. In line with these findings, Liu et al[64] conducted in 2018 a randomized trial in 7 patients with disorder of consciousness using high-frequency rTMS for 2 sessions, each one composed of 5 consecutive days of stimulation separated by 1 week. Only one patient showed an improvement of the Coma Recovery Scale score, shifting from 15 to 23 points[64]. In 2018 Wu et al[65] used theta burst stimulation, a modified form of rTMS that may produce a more powerful and long-lasting effect on cortical excitability. Eight patients with disorder of consciousness experienced a dorsolateral prefrontal cortex stimulation for 5 consecutive days. The Coma Recovery Scale score increased in 4 patients with MCS and in 3 out of 4 patients with UWS at the end of the treatment. The effects persisted 1 week later, showing a long-lasting modification[65]. A larger study including patients with MCS and VS was conducted by Xia et al[66] in 2017. 16 patients received rTMS on the left dorsolateral prefrontal cortex for one session per day over 20 consecutive days[66]. They showed an improvement of functional scales compared to the baseline in all participants, with higher effects in MCS patients[66]. The safety and potential use of TMS in neurorehabilitation has also been tested in pediatric patients. Kirton et al[67] in a preliminary trial conducted in 2008, investigated the use of low frequency rTMS over contralesional motor cortex in 10 children with chronic hemiparesis after subcortical ischemic stroke. Children showed an improvement of motor function in the affected hand with enhanced grip strength[67]. In 2016 Kirton et al[68] conducted a blinded randomized controlled trial to assess the impact of rTMS and constraint-induced movement therapy in addition to intensive rehabilitation therapy in hemiparetic children with MRI-confirmed perinatal stroke. They stated patients involved in intensive rehabilitation programs could accomplish lasting functional benefits through the addition of rTMS[68].

There is widespread consensus among experts that single- and paired-pulse TMS stimulation confer just minimum risk to children[60]. Major risk for rTMS exposure regard seizure, hearing damage, pain and neurocognitive consequences. Future strictly clinical trials are needed to confirm the efficacy of this neurorehabilitative approach on larger samples of children[60].

Discussion

Our review of the current literature showed that NPNS, including SS, music therapy, VR, tDCS and TMS is a promising one in patients with SBI. Many researches have established the positive role of multi-sensory stimulation on the outcome of patients' consciousness, but it is not clear whether more types of stimulation result in greater recovery[69]. In 2020 Zuo et al[70] in their analysis argued that multi-sensory stimulation is better than a single stimulation, but too many types of stimulation do not impact significatively on the recovery. Focusing on the frequency of the stimulus, Padilla et al[71] in 2016 supported that frequent repetitive multi-modal stimulation could successfully benefit clinical outcomes. Conversely, Zuo et al[70] discussed there is no association of frequency and level of consciousness.

The most recent studies highlight the importance of involving family members as main part of stimulation process[72]. Their contribution seems to be relevant and impactful upon the recovery process and neurologic outcome of these patients, mainly in pediatric age, together with the precocity of the clinical stabilization[73].

The studies conducted by Moattari et al[22] and by Salmani et al[23] proved a meaningful impact on patient's outcome comparing stimulation conducted by a family member and by a nurse. Salmani et al[23] showed how the stimulation of the reticular activating system causes an increase of norepinephrine levels and consequently changes the level of consciousness. The family-directed approach to brain injury model is based on principles of hope, family expertise, education/skill building and family-directed intervention[72]. The reason why family-focused stimulation is unique is that it includes emotional stimulation. Affective experience involves subjective thoughts and physiological factors. Thus, it switches the cerebral activity in permanent way. When the stimulus vanishes, a remaining effect persists[74].

One crucial issue is which of NPNS is the best method for treatment of severe brain injury in terms of efficacy and safety. Actually, data are not enough to answer this question. There is not enough evidence on efficacy to recommend for or against any of these techniques.

The drawbacks of our review are included in the limits of the articles we mentioned. The main limitations were: the small sample size each study had, the heterogeneity of study designs, the divergence among the different type of intervention and scales to assess the intervention impact, the short duration of the intervention applied and follow up. Furthermore, the SBI itself was not a standardized category: it included a wide range of varied pathologic conditions distinct by size, anatomical location and clinical features. While the diagnostic criteria for disorders of consciousness have been widely established, there is still a lack of consensus on what is the most efficient assessment tool. For example, the GCS, a widespread scale in the selected articles, lacks items estimating a reaction to brainstem reflexes. Its predictive value can be altered by specific clinical conditions such as sedation or intubation or even by the experience of the assessor[75]. The short duration of the intervention and follow up represents another element of bias. As a matter of fact, the likelihood of spontaneous recovery is maximum in the first phase following the brain damage. Therefore, it becomes more challenging to establish if the outcome is due to neurological stimulation or if it is just a natural process.

Conclusions

Overall, all the non-pharmacological approaches to neurological stimulation in patients with SBI seem to be innovative and promising. Actually, the state of art about these approaches includes drawbacks concerning the few studies done. These involve the short duration of stimulation and follow up, the small samples of patients, the difference of intervention and assessment scales. Further randomized clinical trials including a wide range of patients will be necessary to definitely validate these methods and develop standardized protocols shared in the scientific community.

Conflict of Interest

The Authors declare that there is no conflict of interest.

Authors' Contributions

LDS: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the original article. AC: conception and design of the study, analysis and interpretation of data, making critical revisions related to relevant intellectual content of the manuscript. IC: acquisition of data, analysis and interpretation of data, drafting the original article. LC: acquisition of data, analysis and interpretation of data, drafting the original article. GE: acquisition of data, analysis and interpretation of data, drafting the original article. AG: conception and design of the study, supervision, making critical revisions related to relevant intellectual content of the manuscript, validation and final approval of the version of the article to be published. AC: conception and design of the study, supervision, making critical revisions related to relevant intellectual content of the manuscript, validation and final approval of the version of the article to be published.

Funding Interests

This work was funded by the Italian Ministry of Health Grant: RF-2018-12366594 "Nerve growth factor in pediatric severe traumatic brain injury: translational and clinical studies on a candidate biomarker and therapeutic drug".

ORCID ID

Lorenzo Di Sarno: 0000-0002-4837-9297.

References

1) Khan F, Amatya B, Galea MP, Gonzenbach R, Kesselring J. Neurorehabilitation: applied neuroplasticity. J Neurol 2017; 264: 603-615.
2) Evanson NK, Paulson AL, Kurowski BG. A Narrative Review of Pharmacologic and Non-pharmacologic Interventions for Disorders of Consciousness Following Brain Injury in the Pediatric Population. Curr Phys Med Rehabil Rep 2016; 4: 56-70.
3) Malone LA, Felling RJ. Pediatric stroke: unique implications of the immature brain on injury and recovery. Pediatr Neurol 2020; 102: 3-9.
4) Dennis M. Margaret Kennard (1899-1975): Not a "Principle" of brain plasticity but a founding mother of developmental neuropsychology. Cortex 2010; 46: 1043-1059.
5) Hebb DO. Intelligence, brain function and the theory of mind. Brain 1959; 82: 260-275.
6) Schneider M, Koch M. Behavioral and morphological alterations following neonatal excitotoxic lesions of the medial prefrontal cortex in rats. Exp Neurol 2005; 195: 185-198.
7) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
8) Rosenzweig MR, Bennett EL, Krech D. Supplementary reports cerebral effects of environmental complexity and training among adult rats. J Comp Physiol Psychol 1964; 57: 438-439.
9) Sale A, Berardi N, Maffei L. Enrich the environment to empower the brain. Trends Neurosci 2009; 32: 233-239.
10) Cheng L, Cortese D, Monti MM, Wang F, Riganello F, Arcuri F, Di H, Schnakers C. Do sensory stimulation programs have an impact on consciousness recovery? Front Neurol 2018; 9: 826.
11) Jain R, Karwowski W, Tsytsarev V, Bobrov P, Ramakrishnan AG. Electrophysiological and Neuroimaging Studies – During Resting State and Sensory Stimulation in Disorders of Consciousness: A Review. Front Neurosci 2020; 14: 555093.
12) Mitchell S, Bradley VA, Welch JL, Britton PG. Coma arousal procedure: a therapeutic intervention in the treatment of head injury. Brain Inj 1990; 4: 273-279.
13) Mackay LE, Ma BA, Bernstein PE, Chapman AS, Morgan LS, Milazzo MA. Early Intervention in Severe Head Injury: Long-Term Benefits of a Formalized Program. Arch Phys Med Rehabil 1992; 73: 635-641.
14) Wood RL, Winkowski TB, Miller JL, Tierney L, Goldman L. Evaluating sensory regulation as a method to improve awareness in patients with altered states of consciousness: a pilot study. Brain Inj 1992; 6: 411-418.
15) Lombardi FF, Taricco M, De Tanti A, Telaro E, Liberati A. Sensory stimulation for brain injured individuals in coma or vegetative state. Cochrane Database Syst Rev 2002; CD001427.

16) Oh H, Seo W. Sensory stimulation programme to improve recovery in comatose patients. J Clin Nurs 2003; 12: 394-404.
17) Lotze M, Schertel K, Birbaumer N, Kotchoubey B. A long-term intensive behavioural treatment study in patients with persistent vegetative state or minimally conscious state. J Rehabil Med 2011; 43: 230-236.
18) De Luca R, Pollicino P, Rifici C, De Cola C, Billeri L, Marino S, Trifirò S, Fiumara E, Randazzo M, Bramanti P, Torrisi M. Improving motor and cognitive recovery following severe traumatic brain injury using advanced emotional audio-video stimulation Lessons from a case report. Medicine (Baltimore) 2021; 100.
19) Di Stefano C, Cortesi A, Masotti S, Simoncini L, Piperno R. Increased behavioural responsiveness with complex stimulation in VS and MCS: Preliminary results. Brain Inj 2012; 26: 1250-1256.
20) Tavangar H, Shahriary-Kalantary M, Salimi T, Jarahzadeh M, Sarebanhassanabadi M. Effect of family members' voice on level of consciousness of comatose patients admitted to the intensive care unit: A single-blind randomized controlled trial. Adv Biomed Res 2015; 4: 106.
21) Pape TL, Rosenow JM, Steiner M, Parrish T, Guernon A, Harton B, Patil V, Bhaumik DK, McNamee S, Walker M, Froehlich K, Burress C, Odle C, Wang X, Herrold AA, Zhao W, Reda D, Mallinson T, Conneely M, Nemeth AJ. Placebo-Controlled Trial of Familiar Auditory Sensory Training for Acute Severe Traumatic Brain Injury: a preliminary report. Neurorehabil Neural Repair 2015; 29: 537-547.
22) Moattari M, Shirazi FA, Sharifi N, Zareh N. Effects of a sensory stimulation by nurses and families on level of cognitive function, and basic cognitive sensory recovery of comatose patients with severe traumatic brain injury: A randomized control trial. Trauma Mon 2016; 21: e23531.
23) Salmani F, Mohammadi E, Rezvani M, Kazemnezhad A. The effects of family-centered affective stimulation on brain-injured comatose patients' level of consciousness: A randomized controlled trial. Int J Nurs Stud 2017; 74: 44-52.
24) Bender Pape TL, Livengood SL, Kletzel SL, Blabas B, Guernon A, Bhaumik DK, Bhaumik R, Mallinson T, Weaver JA, Higgins JP, Wang X, Herrold AA, Rosenow JM, Parrish T. Neural Connectivity Changes Facilitated by Familiar Auditory Sensory Training in Disordered Consciousness: A TBI Pilot Study. Front Neurol 2020; 11: 1027.
25) Hotz GA, Castelblanco A, Lara IM, Weiss AD, Duncan R, Kuluz JW. Snoezelen: A controlled multi-sensory stimulation therapy for children recovering from severe brain injury. Brain Inj 2006; 20: 879-888.
26) Eytan D, Pang EW, Doesburg SM, Nenadovic V, Gavrilovic B, Laussen P, Guerguerian AM. Bedside functional brain imaging in critically-ill children using high-density EEG source modeling and multi-modal sensory stimulation. NeuroImage Clin 2016; 12: 198-211.
27) Rauscher FH, Shaw GL, Ky CN. Music and spatial task performance. Nature 1993; 365: 611-611.
28) Chabris CF. Prelude or requiem for the "Mozart effect"? Nature 1999; 400: 826-827.
29) Lancioni GE, Singh NN, O'reilly MF, Sigafoos J, Desideri L. Music Stimulation for People with Disorders of Consciousness: A Scoping Review. Brain Sci 2021; 11: 858.
30) Schnakers C, Magee WL, Harris B, Lindeløv JK, Dienes Z. Sensory Stimulation and Music Therapy Programs for Treating Disorders of Consciousness. Front Psychol 2016; 7: 297.
31) Wu M, Bao WX, Zhang J, Hu YF, Gao J, Luo BY. Effect of acoustic stimuli in patients with disorders of consciousness: a quantitative electroencephalography study. Neural Regen Res 2018; 13: 1900-1906.
32) Särkämö T, Tervaniemi M, Laitinen S, Forsblom A, Soinila S, Mikkonen M, Autti T, Silvennoinen HM, Erkkilä J, Laine M, Peretz I, Hietanen M. Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. Brain 2008; 131: 866-876.
33) Fukui H, Toyoshima K. Music facilitate the neurogenesis, regeneration and repair of neurons. Med Hypotheses 2008; 71: 765-769.
34) Van der Meulen I, Van de Sandt-Koenderman WME, Heijenbrok-Kal MH, Visch-Brink EG, Ribbers GM. The efficacy and timing of melodic intonation therapy in subacute aphasia. Neurorehabil Neural Repair 2014; 28: 536-544.
35) Raglio A, Oasi O, Gianotti M, Rossi A, Goulene K, Stramba-Badiale M. Improvement of spontaneous language in stroke patients with chronic aphasia treated with music therapy: a randomized controlled trial. Int J Neurosci 2016; 126: 235-242.
36) Thaut MH, Mcintosh GC, Hoemberg V. Neurobiological foundations of neurologic music therapy: rhythmic entrainment and the motor system. Front Psychol 2015; 5: 1185.
37) Devlin K, Alshaikh JT, Pantelyat A. Music Therapy and Music-Based Interventions for Movement Disorders. Curr Neurol Neurosci Rep 2019; 19: 83.
38) Thaut MH, Leins AK, Rice RR, Argstatter H, Kenyon GP, McIntosh GC, Bolay HV, Fetter M. Rhythmic Auditory Stimulation Improves Gait More Than NDT/Bobath Training in Near-Ambulatory Patients Early Poststroke: A Single-Blind, Randomized Trial. Neurorehabil Neural Repair 2007; 21: 455-459.
39) Altenmüller E, Marco-Pallares J, Münte TF, Schneider S. Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy. Ann N Y Acad Sci 2009; 1169: 395-405.
40) Kim JH, Park SG, Lim HJ, Park GC, Kim MH, Lee BH. Effects of the Combination of Rhythmic Auditory Stimulation and Task-oriented Training on Functional Recovery of Subacute Stroke Patients. J Phys Ther Sci 2012; 24: 1307-1313.

41) Suh JH, Han SJ, Jeon SY, Kim HJ, Lee JE, Yoon TS, Chong HJ. Effect of rhythmic auditory stimulation on gait and balance in hemiplegic stroke patients. NeuroRehabilitation 2014; 34: 193-199.

42) 42.Merriam-Webster.com Dictionary, s.v. “virtual reality,” accessed April 11, 2022. Available at: https://www.merriam-webster.com/dictionary/virtual%20reality.

43) Deutsch JE, Westcott McCoy S. Virtual Reality and Serious Games in Neurorehabilitation of Children and Adults: Prevention, Plasticity, and Participation. Pediatr Phys Ther 2017; 29: S23.

44) Perez-Marcos D. Virtual reality experiences, embodiment, videogames and their dimensions in neurorehabilitation. J Neuroeng Rehabil 2018; 15: 113.

45) Shen J, Johnson S, Chen C, Xiang H. Virtual Reality for Pediatric Traumatic Brain Injury Rehabilitation: A Systematic Review. Am J Lifestyle Med 2020; 14: 6-15.

46) Christiansen C, Abreu B, Ottenbacher K, Huffman K, Masel B, Culpepper R. Task Performance in Virtual Environments Used for Cognitive Rehabilitation After Traumatic Brain Injury. Arch Phys Med Rehabil 1998; 79: 888-892.

47) Cox DJ, Davis M, Singh H, Barbour B, Nidiffer FD, Trudel T, Mourant R, Moncrief R. Driving Rehabilitation for Military Personnel with TBI Using a Driving Simulator. Mil Med 2010; 175: 411-416.

48) Gamito P, Oliveira J, Pacheco J. Traumatic brain injury memory training: A virtual reality online solution. Int J Disabil Hum Dev 2011; 10: 309-312.

49) Biffi E, Beretta E, Cesareo A, Maghini C, Turconi AC, Reni G, Strazzer S. An immersive virtual reality platform to enhance walking ability of children with acquired brain injuries. Methods Inf Med 2017; 56: 119-126.

50) Choi JY, Yi SH, Ao L, Tang X, Xu X, Shim D, Yoo B, Park ES, Rha DW. Virtual reality rehabilitation in children with brain injury: a randomized controlled trial. Dev Med Child Neurol 2021; 63: 480-487.

51) Keller J, Štětkářová I, Macri V, Kühn S, Pětioký J, Gualeni S, Simmons CD, Arthanat S, Zilber P. Virtual reality-based treatment for regaining upper extremity function induces cortex grey matter changes in persons with acquired brain injury. J Neuroeng Rehabil 2020; 17: 127.

52) Ahorsu DK, Adjaottor ES, Hung Lam BY. Intervention effect of non-invasive brain stimulation on cognitive functions among people with traumatic brain injury: a systematic review and meta-analysis. Brain Sci 2021; 11: 840.

53) Aloi D, Della Rocchetta AI, Ditchfield A, Coulborn S, Fernández-Espejo D. Therapeutic Use of Transcranial Direct Current Stimulation in the Rehabilitation of Prolonged Disorders of Consciousness. Front Neurol 2021; 12: 632572.

54) Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P, Mylius V, Nitsche MA, Padberg F, Palm U, Poulet E, Priori A, Rossi S, Schecklmann M, Vanneste S, Ziemann U, Garcia-Larrea L, Paulus W. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol 2017; 128: 56-92.

55) Stagg CJ, Antal A, Nitsche MA. Physiology of Transcranial Direct Current Stimulation. J ECT 2018; 34: 144-152.

56) Kang EK, Kim DY, Paik NJ. Transcranial direct curent stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: A pilot study. J Rehabil Med 2012; 44: 346-350.

57) Leśniak M, Polanowska K, Seniów J, Członkowska A. Effects of repeated anodal tDCS coupled with cognitive training for patients with severe traumatic brain injury: A pilot randomized controlled trial. J Head Trauma Rehabil 2014; 29: E20-E29.

58) Middleton A, Fritz SL, Liuzzo DM, Newman-Norlund R, Herter TM. Using clinical and robotic assessment tools to examine the feasibility of pairing tDCS with upper extremity physical therapy in patients with stroke and TBI: A consideration-of-concept pilot study. NeuroRehabilitation 2014; 35: 741-754.

59) Sacco K, Galetto V, Dimitri D, Geda E, Perotti F, Zettin M, Geminiani GC. Concomitant use of transcranial direct current stimulation and computer-assisted training for the rehabilitation of attention in traumatic brain injured patients: Behavioral and neuroimaging results. Front Behav Neurosci 2016; 10: 57.

60) Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, Cole L, Godfrey H, Seeger T, Swansburg R, Damji O, Rajapakse T, Hodge J, Nelson S, Selby B, Gan L, Jadavji Z, Larson JR, MacMaster F, Yang JF, Barlow K, Gorassini M, Brunton K, Kirton A. Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. Brain Stimul 2020; 13: 565-575.

61) Burke MJ, Fried PJ, Pascual-Leone A. Transcranial magnetic stimulation: Neurophysiological and clinical applications. Handb Clin Neurol 2019: 73-92.

62) Naro A, Russo M, Leo A, Bramanti P, Quartarone A, Calabrò RS. A Single Session of Repetitive Transcranial Magnetic Stimulation Over the Dorsolateral Prefrontal Cortex in Patients With Unresponsive Wakefulness Syndrome: Preliminary Results. Neurorehabil Neural Repair 2015; 29: 603-613.

63) He F, Wu M, Meng F, Hu Y, Gao J, Chen Z, Bao W, Liu K, Luo B, Pan G. Effects of 20Hz repetitive transcranial magnetic stimulation on disorders of consciousness: A resting-state electroencephalography study. Neural Plast 2018; 5036184.

64) 64. Liu X, Meng F, Gao J, Zhang L, Zhou Z, Pan G, Luo B. Behavioral and resting state function-

al connectivity effects of high frequency rTMS on disorders of consciousness: A sham-controlled study. Front Neurol 2018; 9: 982.

65) Wu M, Wu Y, Yu Y, Gao J, Meng F, He F, Shi J, Luo B. Effects of theta burst stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. Brain Stimul 2018; 11: 1382-1384.

66) Xia X, Bai Y, Zhou Y, Yang Y, Xu R, Gao X, Li X, He J. Effects of 10 Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. Front Neurol 2017; 8: 182.

67) Kirton A, Chen R, Friefeld S, Gunraj C, Pontigon AM, Deveber G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. Lancet Neurol 2008; 7: 507-513.

68) Kirton A, Andersen J, Herrero M, Nettel-Aguirre A, Carsolio L, Damji O, Keess J, Mineyko A, Hodge J, Hill MD. Brain stimulation and constraint for perinatal stroke hemiparesis: The Plastic Champs Trial. Neurology 2016; 86: 1659-1667.

69) Alashram AR, Annino G, Aldajah S, Bani Hamad S, Aliswed B, Padua E. Effects of sensory stimulation on level of consciousness in comatose patients after traumatic brain injury: a systematic review. Physiother Pract Res 2020; 41: 143-153.

70) Zuo J, Tao Y, Liu M, Feng L, Yang Y, Liao L. The effect of family-centered sensory and affective stimulation on comatose patients with traumatic brain injury: a systematic review and meta-analysis. Int J Nurs Stud 2021; 115: 103846.

71) Padilla R, Domina A. Effectiveness of sensory stimulation to improve arousal and alertness of people in a coma or persistent vegetative state after traumatic brain injury: a systematic review. Am J Occup Ther 2016; 70: 7003180030.

72) Fisher A, Bellon M, Lawn S, Lennon S, Sohlberg M. Family-directed approach to brain injury (FAB) model: a preliminary framework to guide family-directed intervention for individuals with brain injury. Disabil Rehabil 2019; 41: 854-860.

73) Chiaretti A, De Benedictis R, Della Corte F, Piastra M, Viola L, Polidori G, Di Rocco C. The impact of initial management on the outcome of children with severe head injury. Childs Nerv Syst 2002; 18: 54-60.

74) Borchardt V, Fan Y, Dietz M, Melendez ALH, Bajbouj M, Gärtner M, Li M, Walter M, Grimm S. Echoes of affective stimulation in brain connectivity networks. Cereb Cortex 2018; 28: 4365-4378.

75) Matis GK, Birbilis T. The Glasgow Coma Scale-A brief review. Past, present, future. Acta Neurol Belg 2014; 108: 75-89.