Behavioural Neurology

Cognitive Neurorehabilitation in Acquired Neurological Brain Injury

Lead Guest Editor: Lambros Messinis

Guest Editors: Mary H. Kosmidis, Grigorios Nasios, Efthymios Dardiotis, and Theodore Tsaousides

Cognitive Neurorehabilitation in Acquired Neurological Brain Injury

Behavioural Neurology

Cognitive Neurorehabilitation in Acquired Neurological Brain Injury

Lead Guest Editor: Lambros Messinis
Guest Editors: Mary H. Kosmidis, Grigorios Nasios, Efthymios Dardiotis, and Theodore Tsaousides

Copyright © 2019 Hindawi Limited. All rights reserved.

This is a special issue published in "Behavioural Neurology." All articles are open access articles distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Editorial Board

Jan Aasly, Norway
Bert Aldenkamp, The Netherlands
Andreas A. Argyriou, Greece
Michael E. Behen, USA
Giuseppe Bellelli, Italy
Ahmad Beydoun, Lebanon
Giuseppe Biagini, Italy
Frederic Blanc, France
Marco Carotenuto, Italy, Italy
Danielle C. Cath, The Netherlands
Ming-Jang Chiu, Taiwan
Leungwing Chu, Hong Kong
Gianluca Coppola, Italy
Dirk Dressler, Germany
Enzo Emanuele, Italy
Luigi Ferini-Strambi, Italy
Pierre O. Fernagut, France
Massimo Filippi, Italy
Othman Ghribi, USA
Cheng-Xin Gong, USA
Tauheed Ishrat, USA
Marjan Jahanshahi, United Kingdom
József Janszky, Hungary
Péter Klivényi, Hungary
Norbert Kovács, Hungary
Cheng-Hsien Lu, Taiwan
Fabio M. Macciardi, USA
Camillo Marra, Italy
Vincent Mok, China
Antonio Orlacchio, Italy
Jesus Pastor, Spain
Barbara Picconi, Italy
Olivier Piguet, Australia
Yolande Pijnenburg, The Netherlands
Antonio Pisani, Italy
Francesco Pisani, Italy
Nikolaos K. Robakis, USA
José J. Rodríguez, Spain
Andrea Romigi, Italy
Guido Rubboli, Denmark
Elisa Rubino, Italy
Hoon Ryu, USA
Shyam S. Sharma, India
Gianfranco Spalletta, Italy
Nicola Tambasco, Italy
Manjari Tripathi, India
Luigi Trojano, Italy
Andrea Truini, Italy
Jian Z. Wang, China
Karsten Witt, Germany
Masahito Yamada, Japan
Mario Zappia, Italy
John H. Zhang, USA

Contents

Cognitive Neurorehabilitation in Acquired Neurological Brain Injury
Lambros Messinis, Mary H. Kosmidis, Grigorios Nasios, Efthymios Dardiotis, and Theodore Tsaousides
Editorial (4 pages), Article ID 8241951, Volume 2019 (2019)

A Neuropsychological Rehabilitation Program for Cognitive Impairment in Psychiatric and Neurological Conditions: A Review That Supports Its Efficacy
Ainara Gómez-Gastiasoro, Javier Peña, Naroa Ibarretxe-Bilbao, Olaia Lucas-Jiménez, María Díez-Cirarda, Oiane Rilo, Genoveva Montoya-Murillo, Leire Zubiaurre-Elorza, and Natalia Ojeda
Review Article (11 pages), Article ID 4647134, Volume 2019 (2019)

Long-Term Follow-Up of Disability, Cognitive, and Emotional Impairments after Severe Traumatic Brain Injury
Britt-Marie Stålnacke, Britt-Inger Saveman, and Maud Stenberg
Research Article (7 pages), Article ID 9216931, Volume 2019 (2019)

Remote Technology-Based Training Programs for Children with Acquired Brain Injury: A Systematic Review and a Meta-Analytic Exploration
Claudia Corti, Viola Oldrati, Maria Chiara Oprandi, Elisabetta Ferrari, Geraldina Poggi, Renato Borgatti, Cosimo Urgesi, and Alessandra Bardoni
Review Article (31 pages), Article ID 1346987, Volume 2019 (2019)

Improving Cognitive Function after Traumatic Brain Injury: A Clinical Trial on the Potential Use of the Semi-Immersive Virtual Reality
Rosaria De Luca, Maria Grazia Maggio, Giuseppa Maresca, Desiree Latella, Antonino Cannavò, Francesca Sciarrone, Emanuele Lo Voi, Maria Accorinti, Placido Bramanti, and Rocco Salvatore Calabrò
Research Article (7 pages), Article ID 9268179, Volume 2019 (2019)

Effects of Systematic Categorization Training on Cognitive Performance in Healthy Older Adults and in Adults with Traumatic Brain Injury
Fofi Constantinidou
Research Article (17 pages), Article ID 9785319, Volume 2019 (2019)

From Broca and Wernicke to the Neuromodulation Era: Insights of Brain Language Networks for Neurorehabilitation
Grigorios Nasios, Efthymios Dardiotis, and Lambros Messinis
Review Article (10 pages), Article ID 9894571, Volume 2019 (2019)

Addressing Evidence Linking Secondary Alexithymia to Aberrant Humor Processing
Panayiotis Patrikelis, Giuliana Lucci, Athanasia Alexoudi, Stefanos Korfias, Lambros Messinis, Grigorios Nasios, Themistoklis Papasilekas, Damianos Sakas, and Stylianos Gatzonis
Review Article (13 pages), Article ID 1803624, Volume 2019 (2019)

Cognitive Rehabilitation of Acquired Calculation Disturbances

Alfredo Ardila and Monica Rosselli

Review Article (6 pages), Article ID 3151092, Volume 2019 (2019)

Hindawi
Behavioural Neurology
Volume 2019, Article ID 8241951, 4 pages
https://doi.org/10.1155/2019/8241951

Editorial

Cognitive Neurorehabilitation in Acquired Neurological Brain Injury

Lambros Messinis,[1] Mary H. Kosmidis,[2] Grigorios Nasios,[3] Efthymios Dardiotis,[4] and Theodore Tsaousides[5]

[1]*Neuropsychology Section, Departments of Neurology and Psychiatry, University Hospital of Patras and University of Patras Medical School, 26504 Patras, Greece*
[2]*Lab of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, Thessaloniki, Greece*
[3]*Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina, Ioannina, Greece*
[4]*Department of Neurology, University of Thessaly Medical School, Larissa, Greece*
[5]*Icahn School of Medicine at Mount Sinai, New York City, USA*

Correspondence should be addressed to Lambros Messinis; lmessinis@upatras.gr

Received 6 September 2019; Accepted 7 September 2019; Published 5 November 2019

Copyright © 2019 Lambros Messinis et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Cognitive impairment is frequent after acquired neurological brain injury (ANBI) and may reduce the ability of a person to adequately process and interpret information, leading to abnormal behaviors, mood disturbances, and dysfunctional adaptive strategy formation. These disabilities may cause profound limitations, affecting daily functional capacity, vocational activities, and socialization [1].

Although a wealth of empirical research has investigated the behavioral and cognitive consequences associated with acquired brain injuries (ABI), relatively less rigorous research has been devoted to investigating their rehabilitation. The main objective of any rehabilitation intervention is to maximize functional recovery and independence, reinstate employment, achieve functional productivity, and improve overall quality of life. Cognitive neurorehabilitation or cognitive rehabilitation (CR) is usually the treatment of choice for impaired cognition and co-occurring behavioral disturbances. Cicerone et al. [2] define CR as "a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding the patients' brain–behavioral deficits."

Cognitive rehabilitation is recognized as a standard component of rehabilitation programs for patients with ABI in many national clinical guidelines (e.g., European Federation of Neurological Sciences) [3]. It is a therapeutic approach aiming to improve cognitive functioning, such as attention, learning and memory, problem solving abilities, and executive function, but also affect and expression [2, 4]. It includes an assembly of methods which attempt to retrain (restore) lost functions or previously established behavioral patterns, with an emphasis in training activities within everyday contexts. Alternatively, compensatory (adaptive) strategies may be taught and applied by the patient or others in order to circumvent their limitations [5]. Addressing the psychological impact and consequences of the brain injury and establishing individual variability patterns are also considered important factors in achieving optimal functional capacity.

In 2002, the National Academy of Neuropsychology (NAN) published an official statement on CR that supports empirically and rationally based CR techniques that have been designed to improve the quality of life and functional outcomes for individuals with ABI (NAN 2002). The American Congress of Rehabilitation Medicine (ACRM), Brain Injury Interdisciplinary Special Interest Group (BI-ISIG), after conducting a systematic review on the impact of cognitive rehabilitation for persons with traumatic brain injury (TBI) or stroke, found a differential benefit favoring CR in almost 80% of all treatment comparisons [2, 6, 7].

Based on these findings, recommendations for clinical practice were formulated accordingly.

CR interventions can usually be applied at all stages of post-injury recovery and in different settings (e.g., inpatient, outpatient, and domestic). Additionally, they can be administered with different modalities (e.g., individual, family, and group) and by healthcare professionals trained in different clinical disciplines (e.g., speech-language therapists-pathologists, clinical neuropsychologists, and occupational therapists) Turner-Stokes et al. [8] investigated multidisciplinary rehabilitation for ABI in adults of working age in a Cochrane review and reported that the context of multidisciplinary rehabilitation appears to positively influence therapeutic outcomes. "Moreover, they found strong evidence" supporting comprehensive CR in a therapeutic environment that involves a peer group of patients.

However, despite previous reports on the positive impact of CR in ABI, the benefits reported are mostly short term and do not generate to everyday contexts. Moreover, systematic reviews generally conclude that the efficacy of CR in ABI, whether of a progressive or nonprogressive nature, is uncertain. In this respect, a systematic review by Koehler et al. [9], found limited, and in some cases, modest evidence that CR is effective for treating some deficits related to traumatic brain injury (TBI), including attention, executive function, social communication, and memory. In 2013, Chung et al. [10] found insufficient evidence that CR interventions were helpful for individuals with executive dysfunction or other secondary outcome measures. More recently, a Cochrane review by Kumar et al. [4] noted that "there is insufficient evidence to support the role of CR when compared to no intervention or conventional rehabilitation in improving return to work, independence in activities of daily living, community integration or quality of life in adults with TBI."

In the most recent and updated systematic review [11] that investigated the relevant clinical literature on the efficacy of CR interventions in persons with TBI from 2009 to 2014, the authors who were members of the Cognitive Rehabilitation Task Force (CRTF) of the ACRM concluded that the evidence obtained supports Practice Standards for (i) attention deficits after TBI or stroke, (ii) visual scanning for neglect after right hemisphere stroke, (iii) compensatory strategies for mild memory deficits, (iv) language deficits after left hemisphere stroke, (v) social-communication deficits after TBI, (vi) metacognitive strategy training for deficits in executive functioning, and (vii) comprehensive-holistic neuropsychological rehabilitation to reduce cognitive and functional disability after TBI or stroke. Although the findings of this recent systematic review provide sufficient evidence to formulate Practice Standards for various CR interventions, the authors note that there is limited evidence that the benefits obtained translate into long-term meaningful changes in patients' everyday functioning capacity. Moreover, specific patient characteristics or models of treatment delivery that impact intervention success are not clearly evident. In this sense, further high-quality research that is directed towards identifying specific patient characteristics (e.g., psychological insight, cognitive reserve, and psychiatric comorbidity) and treatment delivery variables (i.e., intensity and frequency) is an important requirement.

On this background, this special issue entails a series of cutting-edge articles that provide innovative research findings and recent information and advances in the rehabilitation mainly of adults with cognitive, behavioral, or emotional difficulties or disorders resulting from stroke, TBI, or other ABI. We have included original research articles, systematic and Cochrane reviews, and meta-analytic explorations.

Stalnacke et al. from Sweden in an intriguing article investigated through a prospective cohort study the clinical course of disability, cognitive, and emotional impairments in patients aged 18-65 with severe TBI (s-TBI), from 3 months up to 7 years post TBI. The findings of this study are important as most studies of s-TBI focus on the acute phase and then possibly a short follow-up period. In this respect, information regarding the long-term cognitive, emotional, and behavioral outcomes of this heterogeneous clinical population are lacking in the literature. The authors reported that speech and language functions, orientation, attention/concentration, visuospatial and visual problem solving, memory, affect, and awareness as measured by the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) [12] improved significantly from 3 months to 1 year, but not from 1 year to 7 years post TBI. Furthermore, disability status as measured by the 8-category Glasgow Outcome Scale Extended (GOSE) [13] also improved significantly from 3 months to 1 year, but not from 1 year to 7 years post TBI. The findings indicate that s-TBI patients appear to improve during the first year post trauma, and then remain relatively stable at least until the 7th year post trauma. These results highlight the necessity of initially screening for cognitive functions post TBI and then following up with additional assessments over time in order to provide reliable rehabilitation interventions in this population.

De Luca et al. from Italy provide important new data in their compelling article, supporting the ecological validity and efficacy of CR interventions utilizing virtual reality (VR) over traditional CR in patients with TBI. The VR program utilized in this study, according to the authors, offers interactive virtual scenarios and audiovisual stimuli through movement, creating a total sensory involvement that facilitates rehabilitation of attention, visual-spatial, and executive skills. This is carried out with the help of a therapist. Findings of this study showed that cognitive flexibility, shifting skills (i.e., executive functions), and selective attention improved only in the group that received the VR intervention, three sessions a week for 8 weeks compared to the group that received traditional CR. These findings may have implications for the formulation of Practice Standards for CR interventions, possibly directed towards the utilization of more ecologically directed VR-based programs. However, additional evidence from large-scale studies applying VR programs will be necessary in order to investigate whether the benefits obtained translate into long-term meaningful changes in these patients' everyday functioning abilities.

Constantinidou from Cyprus provides us with an appealing article investigating the effects of hierarchical cognitive training using the categorization program (CP) in patients

with TBI, noninjured young adults (18-50), and adults over 60 years old. According to the author, the CP is a rigorous systematic, hierarchical, eight-level program designed as a restorative CR program in adults with ABI. It addresses two distinct areas of human categorization, i.e., passive object recognition and new category learning. Previous research supports its efficacy for adults with ABI who exhibit categorization deficits [14, 15]. Findings of the present research indicated significant improvement in categorization performance in all treated groups, with younger participants, whether healthy or with TBI, demonstrating greater performance gains. Interestingly, a subgroup of older trained adults maintained their positive performance gains for at least four months post intervention. These interesting findings, according to the author, may have implications for how to improve adult cognitive learning and formulate future CR interventions.

Corti et al. from Italy provide an intriguing Systematic Review and Meta-Analytic Exploration on Remote Technology-Based Training programs (RTBP) for children with acquired brain injury. The article provides us with the most recent cognitive and behavioral features and advances related to these types of CR interventions in the child population. The impact of an ABI during childhood is significant, especially with regard to core cognitive functions, behavioral disturbance, social difficulties, and academic performance [16]. Addressing the cognitive and behavioral consequences of ABI in this population becomes a major priority, and RTBP, according to the review and meta-analysis, represent a promising rehabilitation endeavor in this respect. The authors conclude, however, that further rigorous research is required to identify which training characteristics of RTBP and population subgroups may benefit more from such interventions.

Gomez-Gastasoro et al. from Spain focus their interesting article on reviewing the efficacy of an integrative CR program (REHACOP) that provides an integrated bottom-up and top-down approach to rehabilitation, hierarchically organized on an increasing level of difficulty. They stipulate that the application of the program on different neurological populations with cognitive impairment and deficits in social cognition (i.e., multiple sclerosis and Parkinson's disease) and in patients with schizophrenia positively impacted cognition and daily living tasks. The magnitude of improvement ranged from medium to high across the various samples.

Ardilla and. Roselli, from the USA, provided us with an alluring review article on acalculia (or acquired dyscalculia), which according to the authors, is a disturbance in understanding the numerical system associated with the loss of the ability to perform arithmetical operations. The literature related to the rehabilitation of acalculia is relatively limited. Moreover, calculation or numerical difficulties are not commonly evaluated during neuropsychological assessments, despite the fact that acalculia can represent a fundamental acquired cognitive disturbance (primary acalculia). In this respect, this article may provide useful information in order to assist clinicians in rehabilitation settings to address an unmet need.

The compelling review article by Nasios et al. from Greece shifts our attention to the neural networks subserving language and extends from the era of autopsy-driven research with the Broca-Wernicke-Lichtheim-Geschwind classical model to the new model of the functional neuranatomy of language, i.e., the dual stream model. Advances and new insights of language studies in the aging brain and also language in young/developing brains are also critically reviewed. The article further comments on the linkage between language and cognition especially in the elderly, as well as in poststroke aphasia, and the reorganization of language networks in order to provide improved neurorehabilitation strategies for people suffering from neurogenic communication disorders.

Finally, the stirring review article by Patrikelis et al. from Greece explored the current knowledge and assessed the evidence linking secondary (acquired) alexithymia to aberrant humor processing, via their neurobiological mechanisms. Additionally, a possible common neuropathological substrate between secondary alexithymia and deficits in humor appreciation was investigated by drawing on neurophysiologic and neuroradiological evidence, as well as on a recent and unique single-case study which showed the cooccurrence of secondary alexithymia and deficit in humor appreciation. The authors conclude that increased awareness on this topic may assist neurosurgeons when accessing emotion-relevant structures, and for neuropsychologists when formulating evidence-based neurorehabilitative interventions.

From the reports discussed previously and the contributing articles in this special issue, it becomes apparent that significant progress has been achieved in the cognitive rehabilitation of ANBI. Although the efficacy of CR to translate into meaningful long-term changes in ANBI patients' everyday functioning abilities remains uncertain, several important clinical trends are apparent, that require large, high-quality trials, with ecologically valid interventions in order to elucidate patients' everyday functioning capacity. We suggest careful research planning directed towards difficulties in daily life must form the basis for further studies on the efficacy and effectiveness of CR treatment interventions in these diverse clinical population groups.

Conflicts of Interest

The authors report no conflict of interest or private agreements with companies concerning the manuscripts in this Special Issue.

Acknowledgments

The Guest editorial team would like to express their deepest regards to all authors for their valuable and informative high-quality contributions. Moreover, our most sincere appreciation is given to all the reviewers for their endless support and valuable inputs. It has been our privilege to work with all contributing authors and we thank them for their dedication and commitment to advancing the science of cognitive neurorehabilitation. We would also like to thank the journal for hosting and assisting in all aspects in order to make this special issue possible.

Lambros Messinis
Mary H. Kosmidis
Grigorios Nasios
Efthymios Dardiotis
Theodore Tsaousides

References

[1] E. Whyte, E. Skidmore, H. Aizenstein, J. Ricker, and M. Butters, "Cognitive impairment in acquired brain injury: a predictor of rehabilitation outcomes and an opportunity for novel interventions," *PMR*, vol. 3, no. 6, Supplement 1, pp. S45–S51, 2011.

[2] K. D. Cicerone, C. Dahlberg, K. Kalmar et al., "Evidence-based cognitive rehabilitation: recommendations for clinical practice," *Archives of Physical Medicine and Rehabilitation*, vol. 81, no. 12, pp. 1596–1615, 2000.

[3] Members of the Task Force on Cognitive Rehabilitation, S. F. Cappa, T. Benke et al., "EFNS guidelines on cognitive rehabilitation: report of an EFNS task force," *European Journal of Neurology*, vol. 12, no. 9, pp. 665–680, 2005.

[4] K. S. Kumar, S. Samuelkamaleshkumar, A. Viswanathan, A. S. Macaden, and Cochrane Work Group, "Cognitive rehabilitation for adults with traumatic brain injury to improve occupational outcomes," *Cochrane Database of Systematic Reviews*, vol. 6, no. 6, 2017.

[5] R. Koehler, E. E. Wilhelm, and I. Shoulson, *Cognitive Rehabilitation Therapy for Traumatic Brain Injury: Evaluating the Evidence*, National Academies Press, Washington, DC, 2011.

[6] K. D. Cicerone, C. Dahlberg, J. F. Malec et al., "Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 8, pp. 1681–1692, 2005.

[7] K. D. Cicerone, D. M. Langenbahn, C. Braden et al., "Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008," *Archives of Physical Medicine and Rehabilitation*, vol. 92, no. 4, pp. 519–530, 2011.

[8] L. Turner-Stokes, A. Pick, A. Nair, P. B. Disler, D. T. Wade, and Cochrane Injuries Group, "Multi-disciplinary rehabilitation for acquired brain injury in adults of working age," *Cochrane Database of Systematic Reviews*, vol. 22, no. 12, 2015.

[9] R. Koehler, E. Wilhelm, and I. Shoulson, *Cognitive rehabilitation therapy for traumatic brain injury: evaluating the evidence*, National Academies Press, Washington, D.C., 2012.

[10] C. S. Y. Chung, A. Pollock, T. Campbell, B. R. Durward, S. Hagen, and Cochrane Stroke Group, "Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage," *Cochrane Database of Systematic Reviews*, vol. 4, 2013.

[11] K. D. Cicerone, Y. Goldin, K. Ganci et al., "Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014," *Archives of Physical Medicine and Rehabilitation*, vol. 100, no. 8, pp. 1515–1533, 2019.

[12] G. P. Prigatano and J. L. Wong, "Cognitive and affective improvement in brain dysfunctional patients who achieve inpatient rehabilitation goals," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 1, pp. 77–84, 1999.

[13] J. T. L. Wilson, L. E. L. Pettigrew, and G. M. Teasdale, "Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use," *Journal of Neurotrauma*, vol. 15, no. 8, pp. 573–585, 1998.

[14] Y. Brehmer, H. Westerberg, and L. Bäckman, "Working-memory training in younger and older adults: training gains, transfer, and maintenance," *Frontiers in Human Neuroscience*, vol. 6, p. 63, 2012.

[15] F. Constantinidou, R. D. Thomas, V. L. Scharp, K. M. Laske, M. D. Hammerly, and S. Guitonde, "Effects of categorization training in patients with TBI during post-acute rehabilitation: preliminary findings," *The Journal of Head Trauma Rehabilitation*, vol. 20, no. 2, pp. 143–157, 2005.

[16] S. L. Wade, M. E. Narad, E. L. Shultz et al., "Technology-assisted rehabilitation interventions following pediatric brain injury," *Journal of Neurosurgical Sciences*, vol. 62, no. 2, pp. 187–202, 2018.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 4647134, 11 pages
https://doi.org/10.1155/2019/4647134

Review Article

A Neuropsychological Rehabilitation Program for Cognitive Impairment in Psychiatric and Neurological Conditions: A Review That Supports Its Efficacy

Ainara Gómez-Gastiasoro, Javier Peña, Naroa Ibarretxe-Bilbao, Olaia Lucas-Jiménez, María Díez-Cirarda, Oiane Rilo, Genoveva Montoya-Murillo, Leire Zubiaurre-Elorza, and Natalia Ojeda

Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Avenida de las Universidades, 24, 48007 Bilbao, Biscay, Spain

Correspondence should be addressed to Natalia Ojeda; nojeda@deusto.es

Received 15 March 2019; Revised 5 July 2019; Accepted 5 August 2019; Published 21 October 2019

Guest Editor: Lambros Messinis

Copyright © 2019 Ainara Gómez-Gastiasoro et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Neuropsychological rehabilitation has been the focus of much scientific research over the past decades due to its efficacy in different pathologies. Advances in the neuropsychology field have led to improvements and changes in neuropsychological interventions, which in turn have given rise to different approaches and rehabilitation programs. REHACOP is an integrative neuropsychological rehabilitation program designed by specialist neuropsychologists. With an integrated bottom-up and top-down approach, REHACOP includes neurocognition, social cognition, and daily living tasks hierarchically organized on an increasing level of difficulty. Task arrangement is addressed to maximize improvements and transfer effects into participant's daily living. To date, REHACOP has been implemented on different clinical samples such as patients with schizophrenia, multiple sclerosis (MS), and Parkinson's disease (PD). This manuscript presents the efficacy data of REHACOP across these three populations and discusses it in the context of the available literature. Overall, the magnitude of improvements obtained by means of REHACOP ranged from medium to high across samples. These changes were not restricted to specific neurocognitive domains since participants attending the REHACOP program also showed changes in social cognition and daily functioning variables by means of both direct and transfer effects. Results regarding REHACOP's efficacy in psychiatric and neurological conditions have contributed to expanding the existing evidence about the use of structured neuropsychological rehabilitation. In addition, the results obtained after its implementation highlighted the need and importance of designing and implementing integrative neuropsychological rehabilitation programs that are focused not only on cognition *per se* but also on participants' performance in daily living.

1. Introduction

While neuropsychological rehabilitation has been the focus of much scientific research in different disciplines since the late 1970s (see Figure 1), its origins and conceptualization date back to the First and Second World Wars [1–3], and other even remoter roots (Ancient Egypt [4], Paul Broca [5], etc.). As neuropsychology itself, cognitive rehabilitation history is strongly tied to historical medical advances [1–3]. The survival of brain-injured soldiers created the opportunity and the need to work for the recovery of the lost cognitive functions due to focal brain injuries [2]. In light of this, the initial focus of cognitive rehabilitation in its earliest years was traumatic brain injury patients with focal damages. Even at that time (1940s), cognitive rehabilitation was described from an integral approach, involving not only the affected cognitive domain *per se* but also patients' social, functional, and family areas [2]. It was also in that decade when Oliver Zangwill outlined the three principles of cognitive rehabilitation (compensation, substitution, and direct training; [6])

Figure 1: Number of publications including "cognitive rehabilitation" terms in PubMed.

which eventually turned out to be the basis for almost all currently existing cognitive rehabilitation programs.

It was not until the late 1980s and the early 1990s that neuropsychological rehabilitation started to be applied to other neurological conditions, including neurodegenerative diseases such as dementia [7]. This implementation included slight modifications to how neuropsychological rehabilitation was conceptualized and what its aims were, given the course of neurodegenerative diseases. This highlighted the role of cognitive rehabilitation as an instrument for both optimizing and minimizing the extent of a disability, instead of trying to achieve full recovery [7]. From the late 1990s and in the early 21st century, neuropsychological rehabilitation was also implemented in psychiatric patients in an attempt to address those cognitive impairments that could not be treated by either typical or atypical antipsychotics [8–10]. Therefore, neuropsychological rehabilitation principles and techniques have historically shown potential benefits for various brain disorder profiles.

As stated by Wilson [11], neuropsychological rehabilitation has been defined differently over the years, according to the changes and advances in the neuropsychology field. In addition, different concepts related to neuropsychological rehabilitation have also emerged during history. For instance, cognitive rehabilitation is usually broadly defined as a process whereby a brain-injured patient works together with professionals to remediate or alleviate cognitive deficits [3]. A concept that is closely related to neuropsychological rehabilitation is cognitive stimulation, which refers to all those activities that focus on improving general cognitive functioning or some specific domains such as attention, language, or memory [12], with no specific mention to how those activities are organized or structured. Nevertheless, some of those and other terms are usually indistinctly used in the literature, along with other concepts such as cognitive remediation. However, neuropsychological rehabilitation has been proposed as a broader concept than those previously mentioned as it addresses not only cognitive impairments but also those emotional, psychosocial, and behavioral deficits caused by any brain damage in a more or less structured way [3].

1.1. The REHACOP Program. REHACOP (http://rehacop.deusto.es) is an integrative neuropsychological rehabilitation program that was designed by neuropsychology experts at the University of Deusto [13], relying on the knowledge that has been previously generated. The program was originally developed to provide the first available standardized intervention in neuropsychological rehabilitation for Spanish patients with schizophrenia. However, it was later adapted to other clinical populations including neurological conditions such as multiple sclerosis (MS) and Parkinson's disease (PD) [14–17]. Due to the high levels of satisfaction obtained both among patients and therapists, and its efficacy, this manuscript seeks to describe the characteristics of the process involved, as it could be useful for similar interventions elsewhere. REHACOP's specific aims are based on the effective principles of neuropsychological rehabilitation enunciated by Zangwill [6], previously mentioned (Figure 2, [13]).

REHACOP is composed of more than 300 paper-and-pencil tasks using a bottom-up approach (about 85%), and a final integration with top-down tasks (about 15%), following a design that has showed efficacy [18]. This approach highlights the importance of implementing bottom-up approaches in neuropsychological rehabilitation programs in order to have an impact on the basic cognitive processes that have been altered and that could be affecting higher-order functions [19, 20]. Tasks are divided into eight modules, each of which is focused on a specific cognitive domain or area, namely, (a) attention, (b) learning and memory, (c) language, (d) executive functions, (e) social cognition, (f) social skills, (g) activities of daily living, and (h) psychoeducation. The psychoeducation module is focused on the pathology and symptom management. Given that processing speed is a cross-cutting domain, its training takes place along with the first four modules, since a lot of the tasks can be optionally timed. REHACOP is hierarchically organized to provide an order and a bottom-up approach to therapists, so that patients gradually acquire abilities that require building up from the most basic to the most demanding cognitive processes. Both the modules and the tasks included in them are arranged based on an increasing level of difficulty, until it becomes possible for participants to use the skills they have

Figure 2: REHACOP's three basic principles [13].

been trained in their real daily life. As the program allows both individual and group intervention, the therapist can recreate or simulate close to real scenarios to train the patient and facilitate later generalization. This specific arrangement means that the program can facilitate the generalization of trained skills to daily living [13].

The REHACOP program includes both a patient and a therapist manual, so all the materials are in a paper-and-pencil format. This allows subjects to be retrained in skills that are closer to those originally acquired across their lifespan. In the therapist's manual, the professional can find explanatory pages that include the name of the task, information about the cognitive domain and subdomain that the training is focused on, the level of difficulty, the specific instructions for the therapist, the specific instructions to be given to the patient, the necessary materials for each task to be performed, and also an answer sheet with the correct answers to all the tasks [13]. This overall structure facilitates adherence to the underlying principles, which is in the best interest of efficacy and scientific replication.

The recommended time for the implementation of REHACOP in terms of time and frequency is five months, three sessions per week, and (at least) 30-minute sessions for individual interventions and (at least) 90-minute sessions for group interventions, in groups of between 6 and 8 patients with one therapist [13]. Group format was selected due to time and human resource constrictions, allowing the REHACOP implementation in more than one individual in each session. However, efficacy has also been enhanced by having shorter interventions, as will be described later in this paper. Although the first version of REHACOP was in Spanish, the program has now been translated into Portuguese and is currently being translated into English, Polish, and Greek.

For schizophrenia [21], MS [14], and PD [15–17] studies that used REHACOP described in the present review, the intervention lasted for 13 weeks and consisted of three group sessions per week. Each session lasted 60 minutes each for the MS and PD groups and 90 minutes each for the schizophrenia group. The sessions' structure for the schizophrenia, MS, and PD studies was designed and implemented as follows: (1) weeks 1 to 4—attention training (sustained, selective, divided, and shifting attention); (2) weeks 5 to 7—learning and memory training; (3) weeks 8 to 10—language training (grammar, syntax, vocabulary, etc.); (4) weeks 11 to 12—executive function training (planning, analogies, etc.); and (5) week 13—social cognition training. Due to the lack of a social cognition module at the time that the two other schizophrenia studies were performed [22, 23], these did not include social cognition training, whereas the rest of the timetable remained the same. In addition, one of the schizophrenia studies [22] included social skills, activities of daily living, and psychoeducation modules. A summary of the implementation's characteristics and main results is described in Table 1.

2. Implementation of the REHACOP Program in Schizophrenia, Multiple Sclerosis, and Parkinson's Disease

2.1. Schizophrenia. Cognitive impairment has been well described in patients with psychosis and schizophrenia. Their performance has been found to be at least 1 or 1.5 standard deviations below the mean when compared to healthy controls across most of the cognitive domains [24]. However, cognitive deficits are present to a different extent depending on the domain. Some of the most altered domains in patients with schizophrenia are verbal memory, processing speed, language, and nonverbal memory [25–27]. These alterations are present both at the beginning of the disease [26] and at the chronic period [25]. Although to a lesser extent, other cognitive functions such as visuospatial abilities, executive functioning, and working memory are also affected in these patients when their performance is compared to that of normal controls [25, 26]. Furthermore, cognitive deficits have also been described even before the onset of the disease [28, 29] and in naïve patients [30]. Special attention must be paid to basic cognitive processes such as visual or auditory perception, which are also impaired in these patients [31] and might have an important role in the neuropsychological rehabilitation process [19, 20].

Beyond neurocognitive deficits, patients with schizophrenia also show deficits in social cognition [32]. These social cognition alterations seem to be present in all of its four most commonly recognized domains (theory of mind, social

Table 1: Summary of main characteristics of the REHACOP's implementation and significant improvements in each pathology.

Sample	Control group	Group allocation	Duration	Trained modules	Significant improvements after rehabilitation
Schizophrenia 52 REHACOP group vs. 49 control group [21]	Active control group (occupational activities)	Randomized	13 weeks (3 sessions per week, 90 minutes) [21]	(1) Attention, (2) learning and memory, (3) language, (4) executive functions, and (5) social cognition [21]	(i) Neurocognition (ii) Theory of mind, social perception, and emotion processing (iii) Negative symptoms and emotional distress (iv) Functional competence and global functioning
36 REHACOP vs. 48 control group [22]			[22] 13 weeks (3 sessions per week, 90 minutes) [22]	(1) Attention, (2) learning and memory, (3) language, (4) executive functions, (5) social skills, (6) activities of daily living, and (7) psychoeducation [22]	(i) Processing speed, verbal memory, verbal fluency, working memory, and executive functioning (ii) Negative symptoms, disorganization symptoms, and emotional distress (iii) Functional competence, global functioning, and social competence
38 REHACOP vs. 38 control group [23]			12 weeks (3 sessions per week, 90 minutes) [23]	(1) Attention, (2) learning and memory, (3) language, and (4) executive functions [23]	(i) Verbal memory, processing speed, working memory, and verbal fluency (ii) Insight
Multiple sclerosis 21 REHACOP vs. 21 control group [14]	Passive control group	Randomized	13 weeks (3 sessions per week, 60 minutes)	(1) Attention, (2) learning and memory, (3) language, (4) executive functions, and (5) social cognition	(i) Processing speed, working memory, verbal memory, and executive functions
Parkinson's disease 20 REHACOP vs. 22 control group [15]	Active control group (occupational activities)	Randomized	13 weeks (3 sessions per week, 60 minutes)	(1) Attention, (2) learning and memory, (3) language, (4) executive functions, and (5) social cognition	(i) Processing speed and visual memory (ii) Theory of mind (iii) Functional disability

perception, emotion perception, and emotion processing) [32]. However, the magnitude of the deficits is greater in the social perception and theory of mind domains [32].

Neurocognition and social cognition deficits have been found to be strongly related to functional alterations in patients with schizophrenia, especially in the case of social cognition [33]. The strongest associations regarding neurocognition have been found between verbal fluency and community functioning and between verbal learning and memory and social behavior in the milieu [33]. When looking at the relationship between social cognition and functionality, the association between theory of mind and community functioning seems to be the most important, followed by the association between emotion processing and social behavior in the milieu [33].

Brain alterations have been also described in patients with schizophrenia. Regarding anatomical alterations, both gray and white matter volume reductions are described in these patients [27], along with abnormalities in white matter integrity [34]. The latter are mainly circumscribed to frontal and temporal areas located in the left hemisphere [34]. Functional brain alterations have also been described both during performance of a task and at resting state [27]. Studies have related the abnormalities mentioned to cognitive performance and symptoms in these patients, highlighting their role in any rehabilitation process.

2.2. REHACOP in Schizophrenia. Different studies have supported REHACOP's efficacy in improving not only patients' neurocognition [21–23] but also their social cognition [21], clinical symptoms [21, 22], and functionality [21, 22]. Patients on these studies were randomized to the REHACOP or the active control group which performed occupational activities with the same duration and frequency as the REHACOP group (38 patients in the experimental group vs. 38 patients in the active control group [23], 36 patients in the experimental group vs. 48 patients in the active control group [22], and 52 patients in the experimental group vs. 49 patients in the active control group [21]). Patients with schizophrenia receiving REHACOP intervention have shown neurocognitive improvement in processing speed, verbal memory, verbal fluency, working memory, and executive functions [22, 23], as well as in global neurocognition scores [21]. Effect sizes of these improvements have ranged from medium to high depending on the assessed domain with verbal memory and overall cognition showing the largest effects ($d = .88$ and $\eta_p^2 = .14$, respectively) [21, 22]. Among social cognition domains, theory of mind has shown the greatest improvements after implementation ($\eta_p^2 = .15$), followed by social perception ($\eta_p^2 = .08$) and emotion processing ($\eta_p^2 = .07$) [21]. Patients with schizophrenia receiving REHACOP have also shown a decrease in negative ($\eta_p^2 = .08$ and $d = .48$) but not in positive symptoms after the intervention [21, 22].

The REHACOP program has also shown efficacy for improving the social functioning of these patients in a wide range of domains, including functional competence, global functioning, and social competence [21, 22]. This has highlighted the presence of both direct and transfer effects in this pathology. Furthermore, in a more specific study focused on the mechanisms through which REHACOP improved functional outcomes in patients with schizophrenia, functional improvements were found to be mediated by changes in cognition [35]. Specifically, functional outcome changes were mediated by processing speed and verbal memory improvements, but not by improvements in social cognition and negative symptoms [35]. The existence of any brain changes after the implementation of the REHACOP has not yet been studied in this population.

2.3. Multiple Sclerosis. Cognitive impairment is also present in neurological conditions such as MS [36–38]. Cognitive alterations in patients with this pathology include deficits in attention, executive functioning, long-term visual and verbal memory, and visuoconstructive abilities, as well as global cognition [36–38]. Processing speed is also particularly impaired in patients with MS, affecting performance across all other cognitive domains [36]. Deficits have also been described in relation to social cognition, as MS patients have been shown to have difficulty in performing tasks involving theory of mind or emotion processing [39]. As in schizophrenia, cognitive decline has been related to a decreased functional outcome among MS patients. Specifically, the presence of cognitive deficits is related not only to lower performance in daily living and functioning activities but also to reduced social and vocational activities in these patients [36, 40–42]. In addition, cognitive decline has been found to be directly linked to lower quality of life (QoL) indices in MS [36].

Brain abnormalities in MS are present beyond the well-known white matter lesions that characterize the disease. Abnormalities have been described in both normal appearing white and gray matter of these patients, showing cortical and subcortical alterations, pointing mainly to decreased white and gray matter volumes [43]. White matter integrity abnormalities have also been shown in these patients in widespread white matter fibers including intra- and interhemispheric fibers [44]. More recently, functional connectivity abnormalities have also been described in this pathology that affect not only the default mode network but also other resting-state networks such as salience, executive, working memory, sensorimotor, and visual networks [45]. These alterations are related to the cognitive function of these patients and have also shown to be sensitive to change after cognitive rehabilitation [45].

2.4. REHACOP in Multiple Sclerosis. One randomized clinical trial has shown REHACOP's efficacy on improving cognitive impairment in MS [14]. Specifically, patients receiving a 3-month REHACOP group intervention (21 patients) showed improvements in processing speed, working memory, verbal memory, and executive functions when compared with a passive control group (21 patients), which received no neuropsychological intervention [14]. Effect sizes for changes in cognition in this sample were medium-large, and the greatest changes were found in processing speed and working memory ($\eta_p^2 = .16$ and $\eta_p^2 = .15$, respectively) [14]. Although not

significant, performance in attention and verbal fluency showed the same pattern of improvement in the REHACOP group at posttreatment [14]. Neural changes after the implementation of the REHACOP have not yet been published in MS patients.

2.5. Parkinson's Disease. Beyond motor symptoms, cognitive decline in patients with PD has also been well established. PD patients have primarily shown deficits in working and verbal memory, visuospatial abilities, and executive functioning [28, 46–48], as well as in global cognition, in which patients have been found to have lower performance levels when compared to healthy controls [49]. Besides neurocognition, theory of mind deficits have been described among PD patients, being one of the most impaired social cognition domains along with emotion perception [50, 51]. Probably, due to its degenerative character, cognitive deficits show a marked impact on functioning in PD patients, especially regarding activities of daily living and even increasing their disability levels, leading to lower performance levels [52].

Apart from cognitive and functional alterations, PD patients also show brain disturbances at different levels. Gray matter decreases have been described in these patients, mainly in the frontal and temporal areas [53]. Structural abnormalities have also been described regarding both intra- and interhemispheric brain white matter fibers [54]. Beyond structural connectivity, functional connectivity seems to be greatly affected in this pathology and patients show disturbances in different resting-state networks, especially in the connectivity of those areas that comprise the default mode network [55]. These alterations have shown to be related to different cognitive abilities such as perception and executive functions [55].

2.6. REHACOP in Parkinson's Disease. Changes after REHACOP's implementation in PD have been studied both at posttreatment [15, 16] and follow-up [17]. Taking into account the restrained abilities of the participants associated both with age and with the pathology itself (i.e., difficulty in reading, tremors, etc.), some of the tasks were adapted accordingly (i.e., increased font size, oral instead of written tasks, and reduced number of items, etc.). Patients were randomized and included on the REHACOP or the active control group. PD patients receiving REHACOP group intervention (20 patients) exhibited improvements in processing speed, visual memory, theory of mind, and functional disability at posttreatment when compared to the active control group (22 patients) that performed occupational activities during the same period of time and with the same frequency [15]. The largest effect sizes were found for changes in visual memory ($d = .81$), theory of mind ($d = .83$), and functional disability ($d = 1.02$), proving the existence of transfer effects to nontrained domains in this pathology. When assessing REHACOP's efficacy in PD after a longer period of time (18 months; 15 patients included in the experimental group), improvements were found in verbal memory, visual memory, executive functions, theory of mind, and functional disability when comparing baseline and follow-up [17]. In this case, as the control group was not assessed at follow-up, no intergroup comparison was possible. The largest effect sizes were found for changes in theory of mind ($r = .85$) and executive functions ($r = .86$). These studies have reinforced the efficacy of the REHACOP program, not only in the short term but also in the long term at 18-month follow-up, supporting the idea that REHACOP's benefits can be maintained even after the end of the program.

Besides cognition and functionality, the effects of REHACOP on brain connectivity have been studied and described in PD patients [16, 17]. Patients were found to have higher brain activation in the left inferior frontal lobe during a verbal learning task when comparing pre- and posttreatment times, and also a greater activation after the intervention in the left middle temporal area during a verbal recognition task compared to an active control group. In addition, PD patients receiving the intervention (15 patients) showed higher resting-state brain connectivity at posttreatment between the left inferior temporal lobe and the bilateral dorsolateral prefrontal cortex when compared with the active control group (15 patients) [16]. Changes in resting-state brain networks were also found when comparing baseline and follow-up (18 months), with increased activation in frontotemporal networks at follow-up (15 patients in the experimental group and no control group) [17]. However, as expected in the study, no anatomical changes were found after the REHACOP intervention, and both gray and white matter showed a decreased volume and integrity, respectively, in widespread brain areas, following the normal progression of neurodegenerative processes [17]. As in the case of cognitive changes at follow-up, the control group did not undergo the neuroimaging study after 18 months making the comparisons between groups impossible.

3. Discussion

In light of the REHACOP studies mentioned above, some characteristics of the program could be contributing to its efficacy, such as integrating both bottom-up and top-down approaches, having a structured design that includes tasks arranged in a gradually increasing level of difficulty, and also using in vivo tasks. In fact, when reviewing the neuropsychological rehabilitation literature, some of these features have shown to be especially important for the effective design and implementation of different intervention programs [18, 56].

Neurocognitive improvements obtained by means of the REHACOP program in patients with schizophrenia were similar to those described in two of the most recent meta-analyses of neuropsychological rehabilitation in this pathology [57, 58]. Regarding social cognition improvements, both meta-analyses described very similar medium to high effect sizes in overall social cognition changes after intervention. These indices are in line with those obtained after REHACOP's implementation in patients with schizophrenia, except for theory of mind changes, which showed larger effect sizes than the rest of the social cognition domains [21]. This especially good outcome regarding theory of mind could be driven by the specific training of this domain in the social cognition module of the REHACOP, in contrast to

other commonly used cognitive training programs. In addition, changes in clinical symptoms after REHACOP [21, 22] were accompanied by small effect sizes at posttreatment as it has been also described in two recent meta-analyses [57, 58] even when both the experimental and the control groups were equivalent in terms of symptomatology. Moreover, according to those meta-analyses, clinical changes were no longer significant at follow-up assessment [57, 58], which cannot be tested with REHACOP, since there was no follow-up with these patients after treatment was completed. These results, replicated in most of the studies, suggest that cognitive rehabilitation effects on clinical symptoms seem to be temporary and possibly driven by the improvement in cognition or social functioning, especially for negative symptoms.

It is worth noting the functional improvements in these patients that appear in many different domains of functionality, highlighting direct but also transfer effects of other improvements obtained by means of the REHACOP's implementation in patients with schizophrenia.

Given that no studies on brain changes after REHACOP's implementation have been performed in schizophrenia, it is not possible to describe those in the context of the available literature. To date, the effects of cognitive rehabilitation on the brains of patients with schizophrenia have been described regarding both functional and anatomical characteristics. Specifically, changes in resting-state networks such as prefrontal, thalamic, executive, and default mode networks are present in these patients after the implementation of cognitive rehabilitation in one of the latest reviews [59]. Changes in anatomical connectivity are present especially regarding intra- and interhemispheric fibers such as the corpus callosum and the uncinate fasciculus [59]. However, volumetric changes are not so well defined, whereas preservation of gray matter volumes is seen after patients with schizophrenia attended to a cognitive rehabilitation program [59].

The cognitive changes described after REHACOP's implementation in neurological conditions such as MS and PD have provided additional evidence to the existing information about neuropsychological rehabilitation effects in these two pathologies. Specifically regarding MS, two of the latest published reviews [60, 61] have stated that, based on the neuropsychological rehabilitation efficacy studies available to date, there is low-level evidence that neuropsychological rehabilitation reduces cognitive decline in MS patients. However, recent studies show promising results when proving neuropsychological rehabilitation efficacy in MS patients even at the long term [62]. The discrepancy between studies may be due to different factors, including heterogeneity within different forms of the disease. In addition, the intervention format (group vs. individual) could play an important role in terms of finding evidence of improvements. To our knowledge, only one study besides the REHACOP study has assessed the efficacy of cognitive rehabilitation in a group format in MS patients [63]. The individual vs. group approach might account for some of the inconsistencies when trying to find evidence for cognitive rehabilitation efficacy in MS. In addition, some of the cognitive rehabilitation studies in MS do not use an integrative approach and intervene only on one or two specific cognitive domains [64, 65], preventing the transfer effects and significant improvements in the rest of the domains. Therefore, further methodologically rigorous studies are still needed in order to increase the amount of evidence on the efficacy of the neuropsychological rehabilitation in this pathology. Focusing on specific results, one review highlighted improvements in memory span and working memory, with medium effect sizes after neuropsychological rehabilitation [60]. This review also described improvements in attention and immediate and delayed verbal memory, with low-medium effect sizes when combining neuropsychological rehabilitation with other interventions [60]. Results regarding cognitive changes after the implementation of REHACOP in MS patients are in line with this data, but have described medium-to-large effect sizes for all the improvements in cognition [14]. However, in the specific case of the MS sample results, and owing to the lack of an active control group, it is not possible to conclude that all the described improvements are due to the REHACOP's implementation and particularities rather than to more general effects of performing active tasks in a group in contrast to not performing any activity as in the passive control group. One of the aspects highlighted by reviews of neuropsychological rehabilitation and MS is the need to test the efficacy of the interventions, not only in generating cognitive changes but also on promoting brain changes [60, 61]. Although brain changes after the REHACOP's implementation have not yet been studied, the literature points to brain changes after cognitive rehabilitation in MS patients especially regarding functional connectivity of several areas involved in the default mode network [66–68]. However, structural connectivity and specifically volumetric changes are not usually seen in MS after a cognitive intervention [68].

Regarding PD, the REHACOP program has demonstrated long-term effects using neuroimaging techniques in this neurodegenerative disease [17]. Another study has also showed brain changes after cognitive intervention implementation in PD [69]. In that study, results were similar to those obtained by REHACOP, showing increased brain activation at resting state in the left dorsolateral prefrontal cortex and the left superior parietal cortex [69]. Moreover, to our knowledge, REHACOP was the first neuropsychological rehabilitation program that showed significant improvements in both social cognition and functional outcomes of PD patients [15], highlighting the presence of transfer effects in case of functional outcome changes, since this domain was not directly trained. Long-term effects of the neuropsychological rehabilitation have not been widely tested in PD, but the scarce literature available suggests that cognitive changes following intervention are maintained over time [17]. These results emphasize the efficacy of the intervention not only in the short term but also maintained over time, although the lack of assessment of the active control group at follow-up limits this conclusion in relation to REHACOP.

Although the studies described in the current manuscript present similar results in terms of the efficacy of REHACOP, it is challenging to compare specific results between studies. On the one hand, each sample's idiosyncrasy

(neurodevelopmental vs. neurodegenerative diseases, characteristic age of each pathology, characteristic impairment of each sample, etc.) makes it impossible to compare improvements in terms of the effect sizes of enhanced domains or changes. It is therefore difficult to postulate whether REHACOP is a better cognitive intervention for one sample or another, or whether it is more recommendable for one condition or another. On the other hand, differences in the implementation of REHACOP depending on the sample (the extended duration of sessions for patients with schizophrenia, the different modules implemented in each study, or the adaptations made for PD patients) limit the comparability of studies and findings. However, it is notable that the magnitude of the effect sizes and the improved domains depends on the cognitive domains or the pathology. One explanation for these differences could come from differences in the most impaired cognitive domain for each of the pathologies. The highest effect sizes for changes in cognition were found in processing speed in MS, in visual memory in PD, and in verbal memory in schizophrenia, which might be due to the fact that these are some of the most impaired cognitive domains in each condition [25, 36, 46]. Therefore, those specific domains could have greater room for improvement than the others, consequently showing greater changes at the end of the intervention. The characterization of one of the samples as a neurodevelopmental condition (i.e. schizophrenia) and of another as a neurodegenerative condition (i.e. MS and PD) could be generating these differences since neuroplasticity as well as other neurorestorative processes seem to be impaired in neurodegenerative diseases [70]. This could explain the fact that schizophrenia seems to be the sample with the highest number of improved cognitive domains and the highest magnitudes of improvement. Moreover, transfer effects generated by the REHACOP in some of the samples merit further discussion. Significant transfer effects have been described for schizophrenia and PD by means of improvements in functional or daily living areas that were not directly trained, whereas in MS these effects were not described. Thus, improvements in trained domains may not be enough to enhance social functioning in MS patients. In addition, transfer effects could be taking place in those pathologies in which social functioning is more affected by cognitive functioning than by clinical or physical condition, which is usually controlled by pharmacological treatment. Mediational analyses support this hypothesis at least in schizophrenia since functional improvements have shown to be mediated by cognitive improvements but not by improvements in clinical symptoms [35]. This points to the necessity of implementing modules related to social functioning (social skills, activities of daily living, and psychoeducation), at least in MS patients. Finally, the possible effects of implementing a group vs. individual intervention could have had an important role on the obtained results. For example, socializing through the group interaction could account for some of the benefits observed in all the samples included in this review. However, in this specific case, and given that all the active control patients carried out the activities in a group format, group effects that could potentially be affecting the outcomes were controlled. Nevertheless, it is important to take into account the intervention format when analyzing the obtained results after a cognitive rehabilitation implementation since format has been shown to have a role on the benefits obtained [71].

Results and conclusions obtained by means of the REHACOP studies must be seen in the context of some limitations. First, the lack of follow-up studies limits conclusions about the longitudinal effects of REHACOP's implementation in schizophrenia and MS. Future studies should address this issue by means of designing and implementing follow-up interventions. Second, effects of medication on observed improvements should be further assessed, since it has been stated that medications can affect cognition in these pathologies [72–76]. Third, although the REHACOP has been already translated into Portuguese, and it is currently being translated into English, Polish, and Greek, no studies have been carried out in order to assess its efficacy in other countries or languages. This notably limits the inclusion of studies other than those in Spanish that are included in the present review, restricting the efficacy information available.

All of the discussed findings postulate that REHACOP might be an effective integrative neuropsychological rehabilitation program, useful in both psychiatric and neurological patients. One of the specific reasons for its efficacy may be the integrative character of REHACOP. The fact that this program combines the training of cognitive tasks and cognitive strategy training maximizes its impact on participants' benefits. Moreover, the integration of different psychotherapeutic approaches into the intervention favors mutual benefits, which might lead also to a subjective perception of these improvements as it has been shown in a recent meta-analysis [77]. The group and paper-and-pencil format of the program could be a secondary contributing factor to the efficacy of REHACOP. Based on the implementation experience of the REHACOP program, the group format was seen to enhance social interactions between participants and, therefore, participants' efforts to succeed in the tasks, as well as the transfer of different strategies between them. Moreover, the paper-and-pencil character of most of the tasks may foster the improvement of not only the trained task itself (attention, verbal memory, etc.) but also of participants' writing and written expression abilities.

Neuropsychological rehabilitation in general, and specifically REHACOP, could be operating through the same mechanisms that are common to all different conditions such as psychiatric and neurodegenerative pathologies. It is well known that neuroplasticity and synaptic reorganization have a decisive role in neuropsychological rehabilitation effects [56]. Some of the mechanisms involved in both processes have essential implications for rehabilitation, such as diaschisis, functional reorganization, or modification of synaptic connectivity among others [56]. In fact, studies performed using REHACOP have shown brain reorganization at least in PD patients, as described by brain changes occurring after the intervention implementation. These mechanisms, along with other characteristics that have been demonstrated to influence neuropsychological

rehabilitation efficacy (e.g., sociodemographic characteristics, injury-related variables, and psychological factors [56]), might be involved in the common mechanism through which neuropsychological rehabilitation seems to work across pathological conditions. Future studies should address this hypothesis in psychiatric and neurodegenerative diseases, in order to investigate the specific mechanism involved in neuropsychological rehabilitation efficacy.

The evidence presented in this manuscript regarding the multidimensional character of deficits present in psychiatric and neurodegenerative conditions has highlighted the need for integrative neuropsychological rehabilitation programs. The inclusion of psychoeducation and clinical symptom intervention would drive beneficial changes for patients to a greater extent than interventions focused merely on cognitive aspects.

Conflicts of Interest

Natalia Ojeda and Javier Peña are coauthors and copyright holders of the REHACOP neuropsychological rehabilitation program, published by Parima Digital, SL (Bilbao, Spain).

Acknowledgments

Studies included in this review were supported by the Department of Health of the Basque Government (grant number 2011111102 to Dr. Natalia Ojeda and grant number 2011111117 to Dr. Naroa Ibarretxe-Bilbao), the Spanish Ministry of Economy and Competitiveness (grant number PSI2012-32441 to Dr. Naroa Ibarretxe-Bilbao), and the Education Department of the Basque Government (Equipo A) (grant number IT946-16 and grant number BFI-2010-407). The authors would like to thank all the participants and all the associations that took part in the studies.

References

[1] C. Boake, "A history of cognitive rehabilitation of head-injured patients, 1915 to 1980," *The Journal of Head Trauma Rehabilitation*, vol. 4, no. 3, pp. 1–8, 1989.

[2] G. P. Prigatano, "A history of cognitive rehabilitation," in *The Effectiveness of Rehabilitation for Cognitive Deficits*, P. W. Halligan and D. T. Wade, Eds., pp. 3–10, Oxford University Press, New York, NY, US, 2005.

[3] B. A. Wilson, "Neuropsychological rehabilitation," *Annual Review of Clinical Psychology*, vol. 4, no. 1, pp. 141–162, 2008.

[4] B. A. Wilson, "Cognitive rehabilitation in the 21st century," *Neurorehabilitation and Neural Repair*, vol. 16, no. 2, pp. 207–210, 2002.

[5] C. Boake, "Stages in the history of neuropsychological rehabilitation," in *Neuropsychological Rehabilitation: Theory and Practice*, B. A. Wilson, Ed., pp. 11–22, Swets & Zeitlinger, London, United Kingdom, 2005.

[6] O. L. Zangwill, "Psychological aspects of rehabilitation in cases of brain injury," *The British Journal of Psychology General Section*, vol. 37, no. 2, pp. 60–69, 1947.

[7] L. Clare and B. Woods, "A role for cognitive rehabilitation in dementia care," *Neuropsychological Rehabilitation*, vol. 11, no. 3–4, pp. 193–196, 2001.

[8] A. S. Bellack, J. M. Gold, and R. W. Buchanan, "Cognitive rehabilitation for schizophrenia: problems, prospects, and strategies," *Schizophrenia Bulletin*, vol. 25, no. 2, pp. 257–274, 1999.

[9] S. M. Silverstein and S. M. Wilkniss, "At issue: the future of cognitive rehabilitation of schizophrenia," *Schizophrenia Bulletin*, vol. 30, no. 4, pp. 679–692, 2004.

[10] M. F. Green and P. D. Harvey, "Cognition in schizophrenia: past, present, and future," *Schizophrenia Research: Cognition*, vol. 1, no. 1, pp. e1–e9, 2014.

[11] B. A. Wilson, "Towards a comprehensive model of cognitive rehabilitation," *Neuropsychological Rehabilitation*, vol. 12, no. 2, pp. 97–110, 2002.

[12] G. Lubrini, J. A. Periañez, and M. Ríos-Lago, "Estimulación cognitiva y rehabilitación neuropsicológica de la atención," in *Estimulación Cognitiva y Rehabilitación Neuropsicológica*, pp. 35–81, UDC Publishers, Spain, 2009.

[13] N. O. del Pozo, J. P. Lasa, E. B. Noreña et al., "REHACOP: programa de rehabilitación cognitiva en psicosis," *Revista de Neurología*, vol. 54, no. 6, pp. 337–342, 2012.

[14] O. Rilo, J. Peña, N. Ojeda et al., "Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: a randomized clinical trial," *Disability and Rehabilitation*, vol. 40, no. 2, pp. 208–216, 2018.

[15] J. Peña, N. Ibarretxe-Bilbao, I. García-Gorostiaga, M. A. Gomez-Beldarrain, M. Díez-Cirarda, and N. Ojeda, "Improving functional disability and cognition in Parkinson disease randomized controlled trial," *Neurology*, vol. 83, no. 23, pp. 2167–2174, 2014.

[16] M. Díez-Cirarda, N. Ojeda, J. Peña et al., "Increased brain connectivity and activation after cognitive rehabilitation in Parkinson's disease: a randomized controlled trial," *Brain Imaging and Behavior*, vol. 11, no. 6, pp. 1640–1651, 2017.

[17] M. Díez-Cirarda, N. Ojeda, J. Peña et al., "Long-term effects of cognitive rehabilitation on brain, functional outcome and cognition in Parkinson's disease," *European Journal of Neurology*, vol. 25, no. 1, pp. 5–12, 2018.

[18] K. H. Nuechterlein, J. Ventura, K. L. Subotnik, J. N. Hayata, A. Medalia, and M. D. Bell, "Developing a cognitive training strategy for first-episode schizophrenia: integrating bottom-up and top-down approaches," *American Journal of Psychiatric Rehabilitation*, vol. 17, no. 3, pp. 225–253, 2014.

[19] R. A. Adcock, C. Dale, M. Fisher et al., "When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia," *Schizophrenia Bulletin*, vol. 35, no. 6, pp. 1132–1141, 2009.

[20] S. Vinogradov, M. Fisher, and E. De Villers-Sidani, "Cognitive training for impaired neural systems in neuropsychiatric illness," *Neuropsychopharmacology*, vol. 37, no. 1, pp. 43–76, 2012.

[21] J. Peña, N. Ibarretxe-Bilbao, P. Sánchez et al., "Combining social cognitive treatment, cognitive remediation, and functional skills training in schizophrenia: a randomized controlled trial," *NPJ Schizophrenia*, vol. 2, no. 1, 2016.

[22] P. Sánchez, J. Peña, E. Bengoetxea et al., "Improvements in negative symptoms and functional outcome after a new generation cognitive remediation program: a randomized controlled trial," *Schizophrenia Bulletin*, vol. 40, no. 3, pp. 707–715, 2014.

[23] N. O. del Pozo, J. P. Lasa, E. B. Noreña et al., "Evidencias de eficacia de la rehabilitación cognitiva en psicosis y esquizofrenia

con el programa REHACOP," *Revista de Neurología*, vol. 54, no. 10, pp. 577–586, 2012.

[24] R. S. E. Keefe and P. D. Harvey, "Cognitive impairment in schizophrenia," in *Novel Antischizophrenia Treatments*, pp. 11–37, Springer, Berlin, Heidelberg, 2012.

[25] R. W. Heinrichs and K. K. Zakzanis, "Neurocognitive deficit in schizophrenia: a quantitative review of the evidence," *Neuropsychology*, vol. 12, no. 3, pp. 426–445, 1998.

[26] R. I. Mesholam-Gately, A. J. Giuliano, K. P. Goff, S. V. Faraone, and L. J. Seidman, "Neurocognition in first-episode schizophrenia: a meta-analytic review," *Neuropsychology*, vol. 23, no. 3, pp. 315–336, 2009.

[27] N. Ojeda, *Neuropsicología de la esquizofrenia*, Editorial Síntesis, Madrid, Spain, 2018.

[28] H. E. Becker, D. H. Nieman, S. Wiltink et al., "Neurocognitive functioning before and after the first psychotic episode: does psychosis result in cognitive deterioration?," *Psychological Medicine*, vol. 40, no. 10, pp. 1599–1606, 2010.

[29] A. Reichenberg, A. Caspi, H. Harrington et al., "Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study," *The American Journal of Psychiatry*, vol. 167, no. 2, pp. 160–169, 2010.

[30] H. Fatouros-Bergman, S. Cervenka, L. Flyckt, G. Edman, and L. Farde, "Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia," *Schizophrenia Research*, vol. 158, no. 1–3, pp. 156–162, 2014.

[31] F. Ortuño, N. Ojeda, J. Arbizu et al., "Sustained attention in a counting task: normal performance and functional neuroanatomy," *NeuroImage*, vol. 17, no. 1, pp. 411–420, 2002.

[32] G. N. Savla, L. Vella, C. C. Armstrong, D. L. Penn, and E. W. Twamley, "Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence," *Schizophrenia Bulletin*, vol. 39, no. 5, pp. 979–992, 2013.

[33] A.-K. J. Fett, W. Viechtbauer, M.-d.-G. Dominguez, D. L. Penn, J. van Os, and L. Krabbendam, "The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis," *Neuroscience & Biobehavioral Reviews*, vol. 35, no. 3, pp. 573–588, 2011.

[34] I. Ellison-Wright and E. Bullmore, "Meta-analysis of diffusion tensor imaging studies in schizophrenia," *Schizophrenia Research*, vol. 108, no. 1–3, pp. 3–10, 2009.

[35] J. Peña, N. Ibarretxe-Bilbao, P. Sánchez et al., "Mechanisms of functional improvement through cognitive rehabilitation in schizophrenia," *Journal of Psychiatric Research*, vol. 101, pp. 21–27, 2018.

[36] N. D. Chiaravalloti and J. DeLuca, "Cognitive impairment in multiple sclerosis," *The Lancet Neurology*, vol. 7, no. 12, pp. 1139–1151, 2008.

[37] S. Migliore, A. Ghazaryan, I. Simonelli et al., "Cognitive impairment in relapsing-remitting multiple sclerosis patients with very mild clinical disability," *Behavioural Neurology*, vol. 2017, Article ID 7404289, 10 pages, 2017.

[38] R. S. Prakash, E. M. Snook, J. M. Lewis, R. W. Motl, and A. F. Kramer, "Cognitive impairments in relapsing-remitting multiple sclerosis: a meta-analysis," *Multiple Sclerosis*, vol. 14, no. 9, pp. 1250–1261, 2008.

[39] J. Cotter, J. Firth, C. Enzinger et al., "Social cognition in multiple sclerosis: a systematic review and meta-analysis," *Neurology*, vol. 87, no. 16, pp. 1727–1736, 2016.

[40] R. Cutajar, E. Ferriani, C. Scandellari et al., "Cognitive function and quality of life in multiple sclerosis patients," *Journal of Neurovirology*, vol. 6, no. 2, p. S186, 2000.

[41] L. Messinis, P. Papathanasopoulos, M. H. Kosmidis, G. Nasios, and M. Kambanaros, "Neuropsychological features of multiple sclerosis: impact and rehabilitation," *Behavioural Neurology*, vol. 2018, Article ID 4831647, 4 pages, 2018.

[42] S. M. Rao, G. J. Leo, L. Ellington, T. Nauertz, L. Bernardin, and F. Unverzagt, "Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning," *Neurology*, vol. 41, no. 5, pp. 692–696, 1991.

[43] D. H. Miller, A. J. Thompson, and M. Filippi, "Magnetic resonance studies of abnormalities in the normal appearing white matter and grey matter in multiple sclerosis," *Journal of Neurology*, vol. 250, no. 12, pp. 1407–1419, 2003.

[44] S. Roosendaal, J. Geurts, H. Vrenken et al., "Regional DTI differences in multiple sclerosis patients," *NeuroImage*, vol. 44, no. 4, pp. 1397–1403, 2009.

[45] M. Filippi, F. Agosta, E. G. Spinelli, and M. A. Rocca, "Imaging resting state brain function in multiple sclerosis," *Journal of Neurology*, vol. 260, no. 7, pp. 1709–1713, 2013.

[46] A. A. Kehagia, R. A. Barker, and T. W. Robbins, "Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease," *Lancet Neurology*, vol. 9, no. 12, pp. 1200–1213, 2010.

[47] D. Aarsland, K. Bronnick, C. Williams-Gray et al., "Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis," *Neurology*, vol. 75, no. 12, pp. 1062–1069, 2010.

[48] D. Verbaan, J. Marinus, M. Visser et al., "Cognitive impairment in Parkinson's disease," *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 78, no. 11, pp. 1182–1187, 2007.

[49] D. Muslimović, B. Post, J. D. Speelman, and B. Schmand, "Cognitive profile of patients with newly diagnosed Parkinson disease," *Neurology*, vol. 65, no. 8, pp. 1239–1245, 2005.

[50] M. Díez-Cirarda, N. Ojeda, J. Peña et al., "Neuroanatomical correlates of theory of mind deficit in Parkinson's disease: a multimodal imaging study," *PLoS One*, vol. 10, no. 11, article e0142234, 2015.

[51] M. Kawamura and S. Koyama, "Social cognitive impairment in Parkinson's diseas," *Journal of Neurology*, vol. 254, no. 4, pp. -IV49–IV53, 2007.

[52] I. Leroi, K. McDonald, H. Pantula, and V. Harbishettar, "Cognitive impairment in Parkinson disease: impact on quality of life, disability, and caregiver burden," *Journal of Geriatric Psychiatry and Neurology*, vol. 25, no. 4, pp. 208–214, 2012.

[53] P. L. Pan, W. Song, and H. F. Shang, "Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease," *European Journal of Neurology*, vol. 19, no. 2, pp. 199–206, 2012.

[54] C. Atkinson-Clement, S. Pinto, A. Eusebio, and O. Coulon, "Diffusion tensor imaging in Parkinson's disease: review and meta-analysis," *NeuroImage Clinical*, vol. 16, pp. 98–110, 2017.

[55] M. Tahmasian, S. B. Eickhoff, K. Giehl et al., "Resting-state functional reorganization in Parkinson's disease: an activation likelihood estimation meta-analysis," *Cortex*, vol. 92, pp. 119–138, 2017.

[56] M. M. Sohlberg and C. A. Mateer, "Cognitive rehabilitation," in *An Integrative Neuropsychological Approach*, Guilford Publications, 2002.

[57] T. Wykes, V. Huddy, C. Cellard, S. R. McGurk, and P. Czobor, "A meta-analysis of cognitive remediation for schizophrenia:

methodology and effect sizes," *The American Journal of Psychiatry*, vol. 168, no. 5, pp. 472–485, 2011.

[58] S. R. McGurk, E. W. Twamley, D. I. Sitzer, G. J. McHugo, and K. T. Mueser, "A meta-analysis of cognitive remediation in schizophrenia," *The American Journal of Psychiatry*, vol. 164, no. 12, pp. 1791–1802, 2007.

[59] R. Penadés, A. González-Rodríguez, R. Catalán, B. Segura, M. Bernardo, and C. Junqué, "Neuroimaging studies of cognitive remediation in schizophrenia: a systematic and critical review," *World Journal of Psychiatry*, vol. 7, no. 1, pp. 34–43, 2017.

[60] E. M. Rosti-Otajärvi and P. I. Hämäläinen, "Neuropsychological rehabilitation for multiple sclerosi," *Cochrane Database of Systematic Reviews*, vol. 2, 2011.

[61] B. Amatya, F. Khan, L. Ng, M. Galea, and Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group, "Rehabilitation for people with multiple sclerosis: an overview of Cochrane systematic reviews," *Cochrane Database of Systematic Reviews*, vol. 7, 2017.

[62] N. D. Chiaravalloti, N. B. Moore, O. M. Nikelshpur, and J. DeLuca, "An RCT to treat learning impairment in multiple sclerosis: the MEMREHAB trial," *Neurology*, vol. 81, no. 24, pp. 2066–2072, 2013.

[63] H. Brissart, M. Leroy, E. Morele, C. Baumann, E. Spitz, and M. Debouverie, "Cognitive rehabilitation in multiple sclerosis," *Neurocase*, vol. 19, no. 6, pp. 553–565, 2013.

[64] H. Hildebrandt, M. Lanz, H. K. Hahn et al., "Cognitive training in MS: effects and relation to brain atrophy," *Restorative Neurology and Neuroscience*, vol. 25, no. 1, pp. 33–43, 2007.

[65] A. Vogt, L. Kappos, P. Calabrese et al., "Working memory training in patients with multiple sclerosis—comparison of two different training schedules," *Restorative Neurology and Neuroscience*, vol. 27, no. 3, pp. 225–235, 2009.

[66] V. M. Leavitt, G. R. Wylie, P. A. Girgis, J. DeLuca, and N. D. Chiaravalloti, "Increased functional connectivity within memory networks following memory rehabilitation in multiple sclerosis," *Brain Imaging and Behavior*, vol. 8, no. 3, pp. 394–402, 2014.

[67] M. Mitolo, A. Venneri, I. D. Wilkinson, and B. Sharrack, "Cognitive rehabilitation in multiple sclerosis: a systematic review," *Journal of the Neurological Sciences*, vol. 354, no. 1–2, pp. 1–9, 2015.

[68] M. Filippi, G. Riccitelli, F. Mattioli et al., "Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures—an explorative study," *Radiology*, vol. 262, no. 3, pp. 932–940, 2012.

[69] A. Cerasa, M. C. Gioia, M. Salsone et al., "Neurofunctional correlates of attention rehabilitation in Parkinson's disease: an explorative study," *Neurological Sciences*, vol. 35, no. 8, pp. 1173–1180, 2014.

[70] A. M. Enciu, M. I. Nicolescu, C. G. Manole, D. F. Mureşanu, L. M. Popescu, and B. O. Popescu, "Neuroregeneration in neurodegenerative disorders," *BMC Neurology*, vol. 11, no. 1, pp. 1–7, 2011.

[71] T. Ownsworth, J. Fleming, D. Shum, P. Kuipers, and J. Strong, "Comparison of individual, group and combined intervention formats in a randomized controlled trial for facilitating goal attainment and improving psychosocial function following acquired brain injury," *Journal of Rehabilitation Medicine*, vol. 40, no. 2, pp. 81–88, 2008.

[72] K. Seppi, D. Weintraub, M. Coelho et al., "The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease," *Movement Disorders*, vol. 26, Supplement 3, pp. S42–S80, 2011.

[73] A. L. Mishara and T. E. Goldberg, "A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book," *Biological Psychiatry*, vol. 55, no. 10, pp. 1013–1022, 2004.

[74] I. Masahiro, K. Hiroshi, and U. Satoshi, "Can levodopa prevent cognitive decline in patients with Parkinson's disease?," *American Journal of Neurodegenerative Disease*, vol. 6, no. 2, pp. 9–14, 2017.

[75] S. Kapur and G. Remington, "Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia," *Annual Review of Medicine*, vol. 52, no. 1, pp. 503–517, 2001.

[76] C. Christodoulou, P. Melville, W. F. Scherl, W. S. MacAllister, L. E. Elkins, and L. B. Krupp, "Effects of donepezil on memory and cognition in multiple sclerosis," *Journal of the Neurological Sciences*, vol. 245, no. 1-2, pp. 127–136, 2006.

[77] R. Bhome, A. J. Berry, J. D. Huntley, and R. J. Howard, "Interventions for subjective cognitive decline: systematic review and meta-analysis," *BMJ Open*, vol. 8, no. 7, article e021610, 2018.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 9216931, 7 pages
https://doi.org/10.1155/2019/9216931

Research Article

Long-Term Follow-Up of Disability, Cognitive, and Emotional Impairments after Severe Traumatic Brain Injury

Britt-Marie Stålnacke,[1] **Britt-Inger Saveman**,[2] **and Maud Stenberg**[1]

[1]*Department of Community Medicine and Rehabilitation, Rehabilitation Medicine, Umeå University, Umeå, Sweden*
[2]*Department of Nursing, Umeå University, Umeå, Sweden*

Correspondence should be addressed to Britt-Marie Stålnacke; britt-marie.stalnacke@umu.se

Received 28 March 2019; Accepted 16 August 2019; Published 27 August 2019

Guest Editor: Mary H. Kosmidis

Copyright © 2019 Britt-Marie Stålnacke et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Aim. To assess the clinical course of disability, cognitive, and emotional impairments in patients with severe TBI (s-TBI) from 3 months to up to 7 years post trauma. *Methods*. A prospective cohort study of s-TBI in northern Sweden was conducted. Patients aged 18-65 years with acute Glasgow Coma Scale 3-8 were assessed with the Glasgow Outcome Scale Extended (GOSE), the Hospital Anxiety and Depression Scale (HADS), and the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) at 3 months, 1 year, and 7 years after the injury. *Results*. The scores on both GOSE and BNIS improved significantly from 3 months (GOSE mean: 4.4 ± 2.3, BNIS mean: 31.5 ± 7.0) to 1 year (GOSE mean: 5.5 ± 2.7, $p = 0.003$, BNIS mean: 33.2 ± 6.3, $p = 0.04$), but no significant improvement was found from 1 year to 7 years (GOSE mean: 4.7 ± 2.8, $p = 0.13$, BNIS mean: 33.5 ± 3.9, $p = 0.424$) after the injury. The BNIS subscale "speech/language" at 1 year was significantly associated with favourable outcomes on the GOSE at 7 years (OR = 2.115, CI: 1.004-4.456, $p = 0.049$). *Conclusions*. These findings indicate that disability and cognition seem to improve over time after s-TBI and appear to be relatively stable from 1 year to 7 years. Since cognitive function on some of the BNIS subscales was associated with outcome on the GOSE, these results indicate that both screening and follow-up of cognitive function could be of importance for the rehabilitation of persons with s-TBI.

1. Introduction

Traumatic brain injury (TBI) is a major public health problem all over the world and is a leading cause of death and long-term disability in people of working age [1]. The most widely used TBI classification is based on the level of consciousness (LOC) on admission, defined by the Glasgow Coma Scale (GCS) [2]. The annual incidence of all levels of traumatic brain injury (TBI; mild, moderate, and severe according to GCS 3-15) is 250–350,000/year [3–5]. Severe traumatic brain injury (s-TBI) varies between GCS of 3 and 8 on admission; is much rarer, with incidence estimates of 3–12/100,000/year [4]; and has the highest mortality rate [6]. The damage constitutes a major health problem and causes great suffering for both patients and their families with extensive consequences both at the individual and the community level. Patients with s-TBI comprise a heterogeneous group with deficits and impairments of varying complexity that can affect both the physical and mental status as well as social and family life [7]. Cognitive deficits and emotional impairments including symptoms of depression and anxiety have been shown to affect the achievement of rehabilitation goals after TBI and are a major cause of disability after TBI [8]. Since cognitive and emotional impairments are not noticeable initially, it is difficult for other people to understand the severity and problems a person with s-TBI is having to cope with.

Various scales have been developed for the assessment of cognition, depression, anxiety, and disability after TBI. Most studies of cognitive deficits have focused on deficits in memory, attention/concentration, and visuospatial abilities [9, 10], but the impact on a combination of these areas together with affective functions, orientation, and awareness has not been studied to the same extent. The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) is an instrument that has been used to measure both

cognitive and affective disturbances in patients with TBI [11]. The prevalence of depression and anxiety after TBI has been shown to vary widely and may be related to different methods of assessment. One of the most common instruments used in clinical healthcare is the Hospital Anxiety and Depression Scale (HADS) [12] that has been studied in a large number of different patient groups. To measure outcome after s-TBI, the Glasgow Outcome Scale (GOS) is commonly used [13, 14]. This is a global and somewhat crude instrument that only roughly discriminates different levels of disability. A more sophisticated version of the GOS, the Glasgow Outcome Scale Extended (GOSE), has thus been developed, allowing for a more fine-tuned categorisation of posttraumatic disability.

Most studies of s-TBI focus on the acute phase and then a short follow-up period. In a previous national multicentre study of patients with s-TBI (the ProBrain study), we assessed the clinical course of cognitive and emotional function from 3 weeks to 1 year after trauma [15].

In the present study, the aim was to assess the clinical course of patients with s-TBI from northern Sweden (a subgroup of the ProBrain population) on disability, cognitive, and emotional impairments up to 7 years after trauma.

2. Methods

2.1. Design. The design of the study is a prospective cohort study.

2.2. Patients. Inclusion criteria for the study were patients aged 18–65 years, with acute s-TBI with the lowest nonsedated GCS (Glasgow Coma Scale) [2] score 8 of 3–8 within 24 hours post trauma. The exclusion criterion for this study was death within 3 weeks of injury. Thirty-seven patients (11 female, 26 male) with s-TBI were admitted from January 2010 to December 2011 to the Neurotrauma Center (NC) at Umeå University Hospital. These 37 patients were included as part of the Swedish-Icelandic multicentre ProBrain study, a prospective 2-year study with a one-year follow-up of severe traumatic brain injuries [15].

2.3. Procedure. The 37 patients with s-TBI were treated in the acute phase at the Neurotrauma Center (NC) at Umeå University Hospital, covering the North Health Region (NHR) which covers a geographical area which comprises almost half of the total area of Sweden (136,373 km^2). It is divided into four counties and has approximately 900,000 inhabitants, thus comprising only 10% of the total national population. Patients were evaluated at 3 months, 1 year, and up to 7 years after the injury. Assessment took place in the patients' current care setting or at their homes and was performed by the same rehabilitation physician at all time points.

2.4. Instruments

2.4.1. The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS). The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) [11] is a cognitive screening test for speech and language functions, orientation, attention/concentration, visuospatial and visual problem solving, memory, affect, and awareness. BNIS yields a total score and seven subscale scores. The total score (maximum 50 points) reflects overall cognitive function and consists of the results from a prescreen plus the 7 subscale scores (speech and language, 15 points; orientation, 3 points; attention/concentration, 3 points; visual and visuospatial problem solving, 8 points; memory, 7 points; affect, 4 points; and awareness, 1 point). A total subscale score can be obtained. Higher scores reflect a higher level of functioning. If the total BNIS score is below 47 points, further cognitive investigation is recommended. The BNIS has been validated for a Swedish population [16, 17].

2.4.2. The Hospital Anxiety and Depression Scale (HADS). The Hospital Anxiety and Depression Scale (HADS) [12] was used to identify the presence and degree of anxiety and depression. It consists of 14 items (7 items in each subscale, HADS-depression (HADS-D) and HADS-anxiety (HADS-A)) which are assessed on a 4-point Likert scale (range 0-3), where the total score is the sum of each subscale (range 0-21). Cut-offs for both subscales of 8 or higher were used to determine "caseness" [12]. The HADS is an established screening tool for anxiety and depression and it has been used previously in patients with TBI. The HADS has acceptable reliability, sensitivity and specificity in assessing symptom severity in anxiety and depression in various populations [18].

2.4.3. The Glasgow Outcome Scale Extended (GOSE). The Glasgow Outcome Scale Extended (GOSE) [19] extends the 5 categories of the previously developed Glasgow Outcome Scale (GOS) [19] to 8 on disability, thereby increasing its sensitivity. The 8 categories span from "death" (score 1) to "upper good recovery" (score 8). GOSE was also dichotomised into "unfavourable outcome" (GOSE 1-4), and "favourable outcome" (GOSE 5-8). The GOSE has good interrater reliability [19] and validity [20] and is an established measure of global outcome after traumatic brain injury.

3. Statistical Analysis

Data were analysed with SPSS, version 25, for Windows. Data were reported as frequencies or median and means. Nonparametric tests were used as the samples were small and/or not normally distributed. Thus, Wilcoxon's signed-rank test was used for the study of paired observation variables. The level of statistical significance was set as $p = 0.05$. Univariate binary logistic regression analyses were performed to explore associations between the following variables at 1 year: BNIS (total score and the 7 subscale scores), HADS-A, and HADS-D with GOSE as a dependent variable at follow-up after 7 years ("unfavourable and favourable outcomes"). Variables that had a p value < 0.1 in the univariate regression analyses were then included in a multivariate model using a forward method. The results of the logistic regression analyses are presented as an odds ratio (OR). The reliability of the OR is expressed

as a 95% confidence interval (CI). Statistical significance was set at $p < 0.05$ for the multivariate regression analysis.

4. Ethical Considerations

The study has been approved by the Research Ethical Review Board Umeå Sweden, D-nr. 2016/444-31.

5. Results

At the time of follow-up, 9 participants were deceased. Six of them (4 men and 2 women) had died within the first year and three later on. GCS 3 was seen in 9 of the included patients and hospital deaths occurred in 4 of these patients. Two of these patients died at the NC due to respiratory complications, and traumatic and inoperable intracranial aneurysm, respectively. One of the fatalities suffered from multiple illnesses at the time of injury, two of the patients with very severe brain injury (GCS 3) died because of respiratory infection/infection/pneumonia complications, and one patient died from intracerebral bleeding after transportation from NC to the local hospital. Patients with hospital death had a significantly higher mean age in comparison with patients who survived (52.8 ± 17.8 vs. 41.3 ± 15.1, $p = 0.048$).

Thus, there were 28 remaining patients with s-TBI who were eligible to participate in this study. Three participants could not be identified, and four patients declined to participate. Therefore, 21 persons were included in the 7 years follow-up (14 men and 7 women). They were aged between 17 and 64 years at the time of the injury (mean 41 years). Their age varied from 27 to 70 years (median 49) at the time of the follow-up. The median for the lowest nonsedated GCS within 24 hours post trauma was GCS 5 (3-8). Causes of the injury were falls in 9 cases and traffic incidents in 8 cases (Table 1). The participants with s-TBI were hospitalised on average 62 (16-250) days and in a specialised rehabilitation department for an average of 35 (0-127) days.

For background information, see Tables 1 and 2. The number of part-time/full-time workers or being a student had decreased from 17 at time for injury to 10 after 7 years, and participants on full or partial sick leave had increased from 3 to 9. Four participants had personal assistants 24/7 or social care several times daily at follow-up. The ability to keep or get a driving license had decreased from 16 to 13 of the injured participants (Table 2). Eight of the participants with s-TBI had returned to earlier employment or retired. One of the participants with s-TBI also had an incomplete traumatic spinal cord injury but could walk at follow-up.

5.1. GOSE. GOSE improved significantly from 3 months (median 4.5 (1-8), mean: 4.4 ± 2.3) to 1 year (median 7 (1-8), mean: 5.5 ± 2.7; $p = 0.003$) and close to significantly from 3 months and 7 years (median 5 (1-8), mean: 4.7 ± 2.8; $p = 0.059$). No significant improvement was found on GOSE from 1 year to 7 years ($p = 0.137$). At 3 months, GOSE 1-4 was seen in 50% and GOSE 5-8 in 50%. At 1 year, GOSE 1-4 was seen in 36% and GOSE 5-8 in 64%. At 7 years, GOSE 1-4 was seen in 42% and GOSE 5-8 in 58%. Good recovery (GOSE 7-8) was seen in 59%, both at 1 year and at 7 years follow-up (see Table 3).

Table 1: Demographic injury characteristics for persons with severe traumatic brain injury in northern Sweden (approximately 900,000 inhabitants).

	N	%
Included year: 2010-2011	37	100
Included at follow-up	21	57
Age at follow-up ($n = 21$)		
Median 49 (27-70) years		
Gender ($n = 21$)		
Male	14	66
Female	7	33
Diagnosis ($n = 21$)		
S062 diffuse brain injury	6	29
S063 focal brain injury	2	10
S064 EPH	4	19
S065 traumatic SDH	7	33
S066 traumatic SAH	1	5
S068 other	1	5
Influence of alcohol misuse at time of injury	18	
Cause of injury ($n = 21$)	9	43
Fall	8	38
Traffic	3	14
Sport	1	5
Unknown		
Education ($n = 21$)	10	48
<12 years	8	38
12 years	3	14
>12 year		

EPH: epidural hematoma; SDH: subdural hematoma; SAH: subarachnoidal hematoma.

5.2. Hospital Anxiety and Depression Scale-Depression (HADS-D) Scores. No statistically significant differences were found for HADS-D from 3 months (median: 2 (0-10), mean: 3.1 ± 3.0) to 1 year (median: 2.5 (0-12), mean: 3.4 ± 2.5; $p = 0.793$), from 3 months to 7 years (median: 3 (0-11), mean: 3.6 ± 3.0; $p = 0.875$), and from 1 year to 7 years ($p = 0.391$). HADS-D scores above cut-off occurred in 3 participants at 3 months, in 5 participants at 1 year, and in 3 participants at 7 years after injury (see Table 3).

5.3. Hospital Anxiety and Depression Scale-Anxiety (HADS-A) Scores. There was a close to significant difference between the scores of HADS-A from 3 months (median: 3.5 (0-14), mean: 4.5 ± 3.8) to 1 year (median: 4 (0-12), mean: 3.8 ± 3.5; $p = 0.059$), but not from 3 months to 7 years (median: 3 (0-13), mean: 3.7 ± 3.7; $p = 0.373$) and not from 1 year to 7 years ($p = 0.699$). HADS-A scores above cut-off occurred in 5 participants at 3 months, in 4 participants at 1 year, and in 3 participants at 7 years after injury (see Table 3).

Table 2: Marital status, employment and livelihood, personal support, driving license at time of injury (2010-2011) and at follow-up after 7 years ($n = 21$).

	Time of injury		Follow-up after 7 years	
	n	%	*n*	%
Marital status				
Unmarried without underage children living at home	4	19	4	19
Unmarried with underage children living at home	1	5	0	0
Married/cohabitation without underage children living at home	9	43	10	48
Married/cohabitation with underage children living at home	6	29	5	24
Married/cohabitation with grown child living at home	1	5	1	5
Employment				
Working or studying part time or full time	17	81	10	48
Sick leave full time or part time	3	14	9	43
Social care	1	5	1	5
Other	0	0	1	5
Personal support				
Personal assistant 24/7	0	0	2	10
Social care several times daily	0	0	2	10
Driving license	16	76	13	62

Table 3: HADS-depression (HADS-D), HADS-anxiety (HADS-A), and GOSE scores at 3 months, 1 year, and 7 years.

	3 months	1 year	3 months versus 1 year (*p* value)	7 years	3 months versus 7 years (*p* value)	1 year versus 7 years (*p* value)
HADS-D total score median (range)	2 (0-10)	2.5 (0-12)	0.793	3.0 (0-11)	0.875	0.391
HADS-D mean (SD)	3.1 (3.0)	3.4 (2.5)		3.6 (3.0)		
HADS-A total score median (range)	3.5 (0-14)	4 (0-12)	0.059	3.0 (0-13)	0.373	0.699
HADS-A mean (SD)	4.5 (3.8)	3.8 (3.5)		3.7 (3.7)		
$HADS - D \geq 8\%$ (*n*)	12.0 (3)	17.9 (5)	0.694	8.1 (3)		0.442
$HADS - A \geq 8\%$ (*n*)	19.2 (5)	14.3 (4)	0.085	15.0 (3)		0.216
GOSE median (range)	4.5 (1-8)	7 (1-8)	0.003	5 (1-8)	0.059	0.137
GOSE mean (SD)	4.4 (2.3)	5.5 (2.7)		4.7 (2.8)		
GOSE 1-4 (*n* %)	48.6	35.1	0.001	42		0.001
GOSE 5-8 (*n* %)	48.6	64.9		58		

5.4. BNIS. The BNIS total subscale score improved significantly on the paired *t*-tests from 3 months to 1 year post injury ($p = 0.042$). From 1 year to 7 years, no further improvement was found.

No significant improvement on the separate BNIS subscales was shown from 3 months to 7 years after the injury (see Table 4).

5.5. Outcome as Assessed with the Glasgow Outcome Scale Extended (GOSE). In the univariate logistic regression analysis GOSE after 7 years as a dependent variable, several variables 1 year after the injury had a p value < 0.1. Associations (p value < 0.1) were found between the following variables after 1 year and "favourable outcome" on the GOSE: BNIS total subscale score (OR = 1.197, CI: 0.985-1.455, and $p = 0.070$), BNIS subscale speech/language (OR = 2.115, CI: 1.004-4.456, and $p = 0.049$), visuospatial and visual problem solving (OR = 1.765, CI: 0.964-3.232, and $p = 0.066$), and memory (OR = 1.772, CI: 0.933-3.365, and $p = 0.080$). No associations were found between the BNIS subscales orientation, affect, awareness, HADS-A, and HADS-D after 1 year and GOSE at 7 years. The three BNIS subscales

Table 4: BNIS subscale scores and total BNIS scores at 3 months, 1 year, and 7 years.

BNIS score	3 months ($n = 25$) median (range)	1 year ($n = 28$) median (range)	3 months vs. 1 year (p value)	7 years ($n = 13$) median (range)	1 year vs. 7 years (p value)
Speech/language	14 (10-15)	14 (10-15)	0.398	15 (9-15)	0.713
Orientation	3 (1-3)	3 (2-3)	0.317	3 (2-3)	1.000
Attention/concentration	2 (0-3)	2 (1-3)	0.392	2 (1-3)	0.317
Visuospatial and visual problem solving	6 (2-8)	6 (1-8)	0.054	6 (3-5)	0.496
Memory	4 (1-7)	5 (0-7)	0.143	4 (1-6)	0.226
Affect	4 (2-4)	3 (2-4)	0.477	4 (2-4)	0.739
Awareness	1(0-1)	1 (0-1)	0.705	0 (0-1)	0.257
Total BNIS subscale score mean (SD)	31.5 (7.0)	33.2 (6.3)	0.042	33.5 (3.9)	0.424

speech/language, visuospatial and visual problem solving, and memory were incorporated into a multivariate model. The analysis showed that statistically significant associations were only obtained for speech and language (OR = 2.115, CI: 1004-4.456, and $p = 0.049$).

6. Discussion

This study shows that both disability measured with the GOSE and cognition with the BNIS improved significantly from 3 months to 1 year while no further improvement was shown 7 years after the injury.

Nine of the included patients were deceased at the time of follow-up. The majority (six) had died within the first year and three later on. In the group of patients that could be followed up 7 years after the severe traumatic injury, the level of recovery and function varied hugely, from two of the participants having personal assistants all day and night to ten who were working or studying part- or full time. However, the patients who died were older and had lower GCS compared with the survivors. As was the case in previous studies, the majority were males [3, 21]. The severity of TBI on the acute GCS (median GCS) was consistent with other prospective studies of s-TBI [20]. Falls are a common cause of TBI, and in some previous Scandinavian studies, falls have been reported to cause most incidents of s-TBI [3, 21]. Falls were also the most frequent cause of injury in our population of working aged adults. The second most common cause of injury in this study was transport accidents which in American and Australian studies is reported as being the predominant cause [22]. Indications of alcohol use at the time of injury have been shown to be a risk factor for TBI [23, 24]. In our study, almost half were under the influence of alcohol and/or drugs at the time of injury. This is a much higher rate of alcohol use in patients with s-TBI than that reported in a Norwegian study (32%) [25] and in previous studies of patients with m-TBI conducted at the same university hospital as the present study [26]. These findings indicate the existence of high-risk populations and the need for preventive measures.

s-TBI is a heterogeneous group with various deficits and long-term outcomes. This was also shown in our population. Although the patients were initially classified as severe TBI with low GCS scores [2], 1 year after the injury, the overall outcome was encouragingly favourable (GOSE 5-8, 65%) with significantly increased scores on the GOSE. However, this positive trend did not continue over the coming years on the GOSE as the scores had decreased at 7 years. Similar results were found regarding the BNIS at 1 year with higher total scores compared with 3 months but no further improvement. These findings of GOSE recovery plateauing 1 year after the injury are in accordance with the results reported in another study [27] of patients with moderate and severe TBI examined from 3 months to 24 months after the injury. The lower GOSE scores at 7 years could be seen in the concept of TBI as a chronic health condition where factors such as age and preinjury employment may play a role for the long-term outcome [28].

There are probably several reasons for the varying long-term results in the present study. In a previous study of the same population of patients with s-TBI, we studied the clinical pathways 3 months after the severe traumatic injury in the rural area of the North Health Region that covers almost half of Sweden. Most patients were swiftly transported direct to the regional well-monitored neurosurgical and neurointensive care unit. In contrast, the postacute clinical pathways less clearly reflected an optimised medical and rehabilitative strategy. Patients were often transferred back to local hospitals at a fairly early stage [29]. Since subsequent treatment and rehabilitation interventions varied after injury, there were probably no further long-term follow-up strategies from the healthcare services for these patients.

As s-TBI comprises injuries with wide variations as regards complexity of impairments and functional outcomes, prognostic indicators are essential for rehabilitation and treatment.

In a study of prognostic factors for s-TBI after 1 year of the same study population, we used two classification systems of computed tomography (CT) of the brain in the acute phase for prognostication and a prognostic calculator protocol (Corticosteroid Randomisation after Significant Head Injury (CRASH) acute calculator protocol). Neither CT nor CRASH yielded clinically useful predictions of outcome at 1 year post injury [30]. In the present study, the BNIS subscales

speech/language, visuospatial and visual problem solving, and memory at 1 year were significantly or close to significantly associated with "favourable outcome" on the GOSE at follow-up after 7 years. However, in the multivariate model, significant association was only obtained for speech and language. This result is in line with the previous multicentre study ProBrain which reported relationships between some of the BNIS subscales and outcome on the GOSE 1 year after the injury [15].

Although the BNIS scores improved over time in our study, the scores at 1 and 7 years were in a range that was similar to that reported by Swedish TBI patients from a neurorehabilitation clinic [17] which could indicate that the long-term results are probably relatively consistent. However, it is worth remembering that the BNIS is a screening instrument that can be used to detect patients in need of comprehensive cognitive neuropsychological assessment.

This study has several strengths, such as a prospective design and close collaboration as regards case identification, which meant it was possible for most patients to be included. In addition, the extant protocols allowed for referral of patients with a seemingly dismal prognosis. Furthermore, one of the authors (MS) examined all patients at 3 months, at 1 year, and at 7 years and ensured that data were precisely and completely documented, making the amount of missing or secondary data minimal. However, the study is limited by the relatively small study population, of s-TBI, but the subset of this severe group of TBI is rare in comparison with the great majority of mild-moderate TBI. Nevertheless, the included patients comprised a near-total regional cohort population of incident s-TBI patients injured over a period of two years. Most prior studies using the BNIS have used heterogeneous study populations with a mix of diagnoses and different TBI grades [17, 31] which were studied at different time points after the trauma.

A limitation of the study is that not all patients could be followed up, but only three participants could not be identified and another four declined to participate. Another limitation is the heterogeneity of the age of the participants. At follow-up 7 years after the injury, the youngest patient was 27 years old and the oldest was 70 years old. Since outcomes may differ in different age groups, this could be seen as a considerable methodological limitation. However, the study population could reflect the real-life population of persons with s-TBI initially treated at a university hospital.

7. Conclusion

The results indicate that cognition on the BNIS improves over time after s-TBI and appears to be relatively stable from 3 months to 1 year. Since no further improvement was seen at 7 years, the long-term results are probably relatively consistent. Cognitive function on some of the BNIS subscales was associated with outcome on the GOSE. Therefore, it seems that both screening and follow-up of cognitive function could be of importance for the rehabilitation of persons with s-TBI.

Data Availability

The datasets generated and/or analysed in this study are not publicly available as the Ethical Review Board has not approved the public availability of these data.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by grants from the Swedish Association for Survivors of Polio, Accident and Injury.

References

[1] F. Tagliaferri, C. Compagnone, M. Korsic, F. Servadei, and J. Kraus, "A systematic review of brain injury epidemiology in Europe," *Acta Neurochirurgica*, vol. 148, no. 3, pp. 255–268, 2006.

[2] G. Teasdale and B. Jennett, "Assessment of coma and impaired consciousness. A practical scale," *Lancet*, vol. 2, no. 7872, pp. 81–84, 1974.

[3] J. Styrke, B. M. Stålnacke, P. Sojka, and U. Björnstig, "Traumatic brain injures in a well-defined population: epidemiological aspects and severity," *Journal of Neurotrauma*, vol. 24, no. 9, pp. 1425–1436, 2007.

[4] S. Kleiven, P. M. Peloso, and H. Holst, "The epidemiology of head injuries in Sweden from 1987 to 2000," *Injury Control and Safety Promotion*, vol. 10, no. 3, pp. 173–180, 2003.

[5] R. Nguyen, K. M. Fiest, J. McChesney et al., "The international incidence of traumatic brain injury: a systematic review and meta-analysis," *The Canadian Journal of Neurological Sciences*, vol. 43, no. 6, pp. 774–785, 2016.

[6] M. Maegele, R. Lefering, O. Sakowitz et al., "The incidence and management of moderate to severe head injury," *Deutsches Ärzteblatt International*, vol. 116, no. 10, pp. 167–173, 2019.

[7] A. C. Hale, K. M. Bohnert, R. Grekin, and R. K. Sripada, "Traumatic brain injury in the general population," *The Journal of Nervous and Mental Disease*, vol. 207, no. 1, pp. 38–42, 2019.

[8] C. Bornhofen and S. McDonald, "Emotion perception deficits following traumatic brain injury: a review of the evidence and rationale for intervention," *Journal of the International Neuropsychological Society*, vol. 14, no. 4, pp. 511–525, 2008.

[9] S. Sigurdardottir, N. Andelic, E. Wehling et al., "Neuropsychological functioning in a national cohort of severe traumatic brain injury," *The Journal of Head Trauma Rehabilitation*, vol. 30, no. 2, pp. E1–12, 2015.

[10] W. H. A. Ryu, N. K. Cullen, and M. T. Bayley, "Early neuropsychological tests as correlates of productivity 1 year after traumatic brain injury: a preliminary matched case-control study," *International Journal of Rehabilitation Research*, vol. 33, no. 1, pp. 84–87, 2010.

[11] G. P. Prigatano and J. L. Wong, "Cognitive and affective improvement in brain dysfunctional patients who achieve inpatient rehabilitation goals," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 1, pp. 77–84, 1999.

[12] A. S. Zigmond and R. P. Snaith, "The hospital anxiety and depression scale," *Acta Psychiatrica Scandinavica*, vol. 67, no. 6, pp. 361–370, 1983.

[13] B. Jennett, "Assessment of outcome after severe brain damage - a practical scale," *Lancet*, vol. 305, no. 7905, pp. 480–484, 1975.

[14] J. T. King Jr., P. M. Carlier, and D. W. Marion, "Early Glasgow Outcome Scale scores predict long-term functional outcome in patients with severe traumatic brain injury," *Journal of Neurotrauma*, vol. 22, no. 9, pp. 947–954, 2005.

[15] M. Stenberg, A. K. Godbolt, C. Nygren de Boussard, R. Levi, and B. M. Stålnacke, "Cognitive impairment after severe traumatic brain injury, clinical course and impact on outcome: a Swedish-Icelandic study," *Behavioural Neurology*, vol. 2015, Article ID 680308, 12 pages, 2015.

[16] V. Denvall, S. Elmstahl, and G. P. Prigatano, "Replication and construct validation of the Barrow Neurological Institute Screen for Higher Cerebral Function with a Swedish population," *Journal of Rehabilitation Medicine*, vol. 34, no. 4, pp. 153–157, 2002.

[17] C. Hofgren, E. Esbjornsson, H. Aniansson, and K. S. Sunnerhagen, "Application and validation of the Barrow Neurological Institute Screen for Higher Cerebral Functions in a control population and in patient groups commonly seen in neurorehabilitation," *Journal of Rehabilitation Medicine*, vol. 39, no. 7, pp. 547–553, 2007.

[18] I. Bjelland, A. A. Dahl, T. T. Haug, and D. Neckelmann, "The validity of the Hospital Anxiety and Depression Scale," *Journal of Psychosomatic Research*, vol. 52, no. 2, pp. 69–77, 2002.

[19] J. T. L. Wilson, L. E. L. Pettigrew, and G. M. Teasdale, "Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use," *Journal of Neurotrauma*, vol. 15, no. 8, pp. 573–585, 1998.

[20] H. S. Levin, C. Boake, J. Song et al., "Validity and sensitivity to change of the Extended Glasgow Outcome Scale in mild to moderate traumatic brain injury," *Journal of Neurotrauma*, vol. 18, no. 6, pp. 575–584, 2001.

[21] N. Andelic, A. Anke, T. Skandsen et al., "Incidence of hospital-admitted severe traumatic brain injury and in-hospital fatality in Norway: a national cohort study," *Neuroepidemiology*, vol. 38, no. 4, pp. 259–267, 2012.

[22] P. G. Harradine, J. B. Winstanley, R. Tate, I. D. Cameron, I. J. Baguley, and R. D. Harris, "Severe traumatic brain injury in New South Wales: comparable outcomes for rural and urban residents," *The Medical Journal of Australia*, vol. 181, no. 3, pp. 130–134, 2004.

[23] R. C. Opreanu, D. Kuhn, and M. D. Basson, "Influence of alcohol on mortality in traumatic brain injury," *Journal of the American College of Surgeons*, vol. 210, no. 6, pp. 997–1007, 2010.

[24] C. M. Chen, H. Y. Yi, Y. H. Yoon, and C. Dong, "Alcohol Use at Time of Injury and Survival Following Traumatic Brain Injury: Results From the National Trauma Data Bank," *Journal of Studies on Alcohol and Drugs*, vol. 73, no. 4, pp. 531–541, 2012.

[25] N. Andelic, E. Bautz-Holter, P. Ronning et al., "Does an early onset and continuous chain of rehabilitation improve the long-term functional outcome of patients with severe traumatic brain injury?," *Journal of Neurotrauma*, vol. 29, no. 1, pp. 66–74, 2012.

[26] B. M. Stålnacke, U. Björnstig, K. Karlsson, and P. Sojka, "One-year follow-up of mild traumatic brain injury: post-concussion symptoms, disabilities and life satisfaction in relation to serum levels of S-100B and neurone-specific enolase in acute phase," *Journal of Rehabilitation Medicine*, vol. 37, no. 5, pp. 300–305, 2005.

[27] M. Sandhaug, N. Andelic, B. Langhammer, and A. Mygland, "Functional level during the first 2 years after moderate and severe traumatic brain injury," *Brain Injury*, vol. 29, no. 12, pp. 1431–1438, 2015.

[28] M. V. Forslund, P. B. Perrin, C. Røe et al., "Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury," *Frontiers in Neurology*, vol. 10, p. 219, 2019.

[29] M. Stenberg, L. O. Koskinen, R. Levi, and B. M. Stålnacke, "Severe traumatic brain injuries in Northern Sweden: a prospective 2-year study," *Journal of Rehabilitation Medicine*, vol. 45, no. 8, pp. 792–800, 2013.

[30] M. Stenberg, L. O. D. Koskinen, P. Jonasson, R. Levi, and B. M. Stålnacke, "Computed tomography and clinical outcome in patients with severe traumatic brain injury," *Brain Injury*, vol. 31, no. 3, pp. 351–358, 2017.

[31] S. R. Borgaro, G. P. Prigatano, C. Kwasnica, S. Alcott, and N. Cutter, "Disturbances in affective communication following brain injury," *Brain Injury*, vol. 18, no. 1, pp. 33–39, 2004.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 1346987, 31 pages
https://doi.org/10.1155/2019/1346987

Review Article

Remote Technology-Based Training Programs for Children with Acquired Brain Injury: A Systematic Review and a Meta-Analytic Exploration

Claudia Corti,[1] Viola Oldrati,[1] Maria Chiara Oprandi,[1] Elisabetta Ferrari,[1] Geraldina Poggi,[1] Renato Borgatti,[1] Cosimo Urgesi,[1,2,3] and Alessandra Bardoni[1]

[1]*Scientific Institute, IRCCS E. Medea, Bosisio Parini, Lecco, Italy*
[2]*Laboratory of Cognitive Neuroscience, Department of Languages and Literatures, Communication, Education and Society, University of Udine, Italy*
[3]*Scientific Institute, IRCCS E. Medea, San Vito al Tagliamento, Pordenone, Italy*

Correspondence should be addressed to Claudia Corti; claudia.corti@lanostrafamiglia.it

Received 15 March 2019; Revised 17 May 2019; Accepted 11 June 2019; Published 1 August 2019

Guest Editor: Lambros Messinis

Copyright © 2019 Claudia Corti et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction. Multidisciplinary rehabilitation interventions are considered to be a need for children with acquired brain injury (ABI), in order to remediate the important sequelae and promote adjustment. Technology-based treatments represent a promising field inside the rehabilitation area, as they allow delivering interventions in ecological settings and creating amusing exercises that may favor engagement. In this work, we present an overview of remote technology-based training programs (TP) addressing cognitive and behavioral issues delivered to children with ABI and complement it with the results of a meta-analytic exploration. *Evidence Acquisition*. We performed the review process between January and February 2019. 32 studies were included in the review, of which 14 were further selected to be included in the meta-analysis on TP efficacy. *Evidence Synthesis*. Based on the review process, the majority of TP addressing cognitive issues and all TP focusing on behavioral issues were found to be effective. Two meta-analytic models examining the means of either cognitive TP outcomes or behavioral TP outcomes as input outcome yielded a nonsignificant effect size for cognitive TP and a low-moderate effect size for behavioral TP. Additional models on outcomes reflecting the greatest beneficial effects of TP yielded significant moderate effect sizes for both types of TP. Nevertheless, consistent methodological heterogeneity was observed, pointing to cautious interpretation of findings. A subgroup analysis on visuospatial skill outcomes showed a smaller yet significant effect size of cognitive TP, with low heterogeneity, providing a more reliable estimation of overall cognitive TP effects. *Conclusions*. Promising results on remote cognitive and behavioral TP efficacy emerged both at the review process and at the meta-analytic investigation. Nevertheless, the high heterogeneity that emerged across studies prevents us from drawing definite conclusions. Further research is needed to identify whether specific training characteristics and population subgroups are more likely to be associated with greater training efficacy.

1. Introduction

Pediatric acquired brain injuries (ABI) are insults to the central nervous system that occur after birth. The nature of this damage can be traumatic or nontraumatic (infection, stroke, hypoxia, brain tumors, neurosurgery, and other central nervous system treatments [1]). Traumatic brain injury (TBI) is the most frequent cause of ABI in childhood [2], affecting more than 3 million children worldwide every year [3] and representing a considerable portion of all neurologic disabilities [4].

Children with ABI are often reported to exhibit deficits in various cognitive domains, including intellectual functioning, core cognitive abilities, and visual-related processes [2, 5–7]. Even those children who keep an intellectual quotient within the normal range often experience difficulties in achieving academic success after the event [8, 9]. Deficits in neuropsychological abilities affecting social competence

and psychosocial and behavioral concerns have also been documented [10, 11]. Anomalies in cognitive, behavioral, and social domains have been reported regardless of injury severity, thus affecting the majority of children [12]. All these deficits cause a negative impact on children's adjustment in daily life [13]. Consequently, rehabilitation treatments to improve cognitive and behavioral functioning have been considered necessary for sustaining recovery and adjustment of these patients [12, 14].

In the last two decades, numerous papers on rehabilitation treatments for pediatric ABI or reviews on the topic have been published [1, 12, 14–20]. However, it has not been yet clarified which are the most effective interventions. This could be associated with methodological shortcomings of the study design, such as lack of control group or small sample size, or to the heterogeneity of the population selected for the study (in terms of age at the event, time since the event, diagnosis, etc.), or even to the variety of instruments used to assess outcomes [12, 17].

A review of Lindsay and colleagues [16] described hospital-to-school reintegration interventions for pediatric ABI, including treatments addressing cognitive or behavioral impairments, interventions delivered by a clinician in the clinical setting, home-based or web-based interventions, family or social support programs, and art-based activities. The Authors identified some possible components of successful interventions, such as one-to-one sessions conducted by a therapist or educator, the involvement of parents, and homework activities. However, they also reported that a significant improvement could be observed after online home-based interventions addressing cognitive and behavioral aspects [21–23]. This pointed to positive gains associated with computer-based treatments performed out of the clinical setting and with limited participation of a therapist.

Linden and colleagues [14, 15] performed two meta-analyses on web-based training programs (TP) for pediatric ABI. The meta-analysis focusing on neuropsychological outcomes [15] was based on three studies from the same research team applying web-based interventions for everyday executive functions and found positive treatment effects on self- and/or parent-report measures on everyday behavioral problems associated with executive dysfunction. However, potential sources of methodological biases were reported. On the contrary, the meta-analysis focusing on academic achievement [14] found no training effect. Nevertheless, the small number of participants in the included studies and the variety of measures adopted to assess outcomes were indicated as potential factors limiting the validity of conclusions.

A recent review of Resch and colleagues [17] provided an overview of the studies that described cognitive rehabilitation interventions for ABI in pediatric age, examining their specific components and distinguishing them as (1) metacognition and/or strategy use; (2) computerized drill-based exercises; (3) interventions combining metacognition and/or strategy use and drill-based exercises; and (4) external aids. Overall, this work indicated that metacognition and/or strategy-use interventions may produce benefits for adaptive behavior but have limited effects for cognitive functions. In contrast, computerized drill-based exercises seem to generate only near-transfer gains, namely in those outcomes that are similar to the training tasks, while far transfer does not emerge either in the global cognitive domain or in more general executive-function behavior or adaptive behavior. The Authors suggested that such results could be in part attributed to short training duration and short training time. The simultaneous adoption of both metacognition/strategy-use and computerized drill-based training was identified as the most effective way to improve cognitive and psychosocial impairments. External aids were reported to generate benefits in everyday cognitive functions, particularly when they are used in combination with metacognition/strategy use. Finally, the provision of the interventions in family- or peer-supported settings was indicated to be a potential factor leading to better outcomes.

In a similar vein, Wade and colleagues [12] described technology-assisted interventions for pediatric patients with ABI, focusing on both treatments delivered at a distance and treatments included in the traditional rehabilitation setting to promote engagement and improve efficacy. Overall, the most positive results were reported for those interventions providing family-centered, online problem-solving aimed at ameliorating behavioral issues. In three subsequent meta-analytic explorations from the same research group, these interventions were found to be more effective when being delivered at longer time since injury and to children of older age (in front of an age range of 5-18 years), with lower intellectual quotient and whose parents had lower education [24–26]. Treatments for attention, working memory, and executive functioning were also described as promising, but methodological limitations of studies were highlighted. Furthermore, commercially available games were indicated as alternatives to support physical and occupational therapy, while training in the use of social media and app-based goal setting were described as having the potential advantage to promote social engagement.

Taken together, the cited reviews indicated the use of technology as a promising method to implement rehabilitation interventions for children with ABI, even though they warned about the fact that definite conclusions are hampered by methodological issues, such as heterogeneity in patients and outcomes and lack of control groups. These reviews included a complete and updated overview of the treatments for ABI but did not distinguish between treatments delivered in a clinical setting and those delivered remotely. The use of remote interventions has consistently increased in recent years [27, 28] with the aim to overcome the limits associated with traditional interventions, such as high time demand, elevated costs, accessibility issues, and heterogeneity in treatment practices. Remote TP may increase opportunities and consistency of rehabilitation for patients, limiting time and economic demands for them and their families, and may also promote engagement, introducing amusing exercises by using computer-based platforms [12, 29]. In view of the peculiar characteristics of remote TP, evaluating the effects of these interventions, distinguishing them from those delivered in a traditional clinical setting, should be considered a matter of interest. For this reason, different from the reviews described above, the present review focused on the effects of

TP for pediatric ABI that were delivered in an ecological setting only and that did not require the intervention of a therapist at all or that required it only to a limited extent (at most, once a week).

Remote TP with either a cognitive or a behavioral focus were considered for this work. However, due to the methodological differences between the two types of interventions, cognitive and behavioral TP were examined separately. In fact, cognitive TP were composed of drill-based exercises aimed at stimulating different cognitive domains and required solely the involvement of patients. In most studies, the therapist intervention was limited to monitor training adherence, while in a few studies it was aimed at providing weekly feedback on patient's performance and cognitive strategies. In contrast, behavioral TP consisted of self-guided didactic content on problem-solving abilities and on exercises to practice these skills and were performed by the patient together with family or with the remote support of a peer. Moreover, for most behavioral TP, every one to two weeks a therapist performed a remote videoconference session with the patients and families to give a feedback on the implementation of the problem-solving process in real life. Nevertheless, despite methodological differences associated with program activities and procedures, both types of treatments were designed to be completed by the patients at home, with the aim to limit family burden associated with visiting a clinic and to ensure easier access to rehabilitation treatments.

In keeping with aforementioned reviews, we included both randomized and nonrandomized controlled studies: in fact, previous research found that these two study procedures produce similar effect sizes [30, 31]. The search strategy we adopted to detect eligible records led us to include studies that were not considered in any previous reviews, ensuring a more comprehensive overview of remote interventions for pediatric ABI. A further innovative characteristic of this work is that we also performed a meta-analytic exploration on those studies including a control group, in order to provide an overall estimation of the mean effect of TP. Such an investigation allowed us to obtain evidence-based data on treatments for pediatric ABI, which has been reported to be a need by the Recommendations for Research of the Centers for Disease Control and Prevention [32].

2. Method

2.1. Study Selection for Review and Meta-Analysis. A literature search was conducted using scientific online databases (PubMed and Scopus) to identify pertinent studies, using the terms: *brain injury* AND (*rehabilitation* OR *training*) AND (*home* OR *school*) and (*children* OR *pediatric* OR *adolescents*). The period of time considered for study inclusion ranged from January 2000 to December 2018. We excluded studies published before 2000 to limit the search to more advanced technology-based programs. Additionally, the published article databases of Cogmed Working Memory Training, Lumosity Cognitive Training, and Brain Training software programs were browsed through their websites. Reviews on the topic obtained from search process on PubMed and Scopus were screened to minimize the risk of overlooking or missing out potentially suitable studies for inclusion [12, 14–17].

Criteria for inclusion for study selection were the following: (i) children and adolescents (aged < 21 years old) (US Department of Health and Human Services Food and Drug Administration Guidance for Industry and FDA Staff: Pediatric Expertise for Advisory Panels. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health; 2003.); (ii) diagnosis of ABI (e.g., TBI, brain infection, anoxia, and cancer-related injury); (iii) usage of remotely delivered technology-based intervention programs; (iv) limited intervention of clinicians (no more than 1 hour per week); (v) performance-based cognitive measures or rating-scale behavioral indexes as primary outcomes for TP addressing cognitive or behavioral aspects, respectively; and (vi) articles published in peer-reviewed English-language journals.

Only studies with a group-controlled design and reporting immediate post-training outcomes were considered for inclusion in the meta-analytic exploration (the study by Treble-Barna and colleagues [33] compared an experimental group with sex- and age-matched healthy controls performing the same training. Thus, given the different diagnoses and the lack of a passive control group or an active control group performing a low-demanding training, this study was not included in the meta-analytic examinations). If an article reported both immediate post-treatment and follow-up measures, only immediate post-training outcomes were selected. Congruently, if an article reported follow-up data of a previous study, only data from the first published study was extracted. This choice was made as some studies either did not report any follow-up measures at all or reported follow-up measures taken at different time points since treatment completion. This limits heterogeneity, as effects associated with receiving a treatment may change over time.

We excluded from both the review and the meta-analytic exploration studies: (i) applying rehabilitation programs with an exclusive focus on motor skills, (ii) reporting feasibility and acceptability measures only, (iii) assessing the effects of interventions tailored to parents, (iv) assessing the effects of interventions tailored to children and parents, but reporting outcomes of only parents; (v) clinician-delivered, and (vi) testing the usage of external aids (reminder messages, diaries, etc.). On a related note, the study of de Kloet and colleagues [34] included a subgroup of participants exceeding the age limit. However, since the majority of patients ranged between 8 and 18 years old, we decided to include the study in this work. For those studies on behavioral TP reporting outcomes on both children and parents, we collected only outcomes related to children.

The extent of support provided by clinicians during the rehabilitation practice was case-wise evaluated to check study eligibility. If an intervention implied weekly contact with clinicians to assess adherence and/or resolve any type of problems that occurred in performing the TP, it was evaluated as eligible. Otherwise, if a training required the presence and continuative support of a clinician, it was not considered for inclusion. Three studies [34–36] indicated clinic as one of the possible settings where the intervention could be held,

but they described interventions primarily feasible for ecological settings (i.e., home or school) and were, thus, evaluated eligible for inclusion in this work.

For the meta-analysis on cognitive TP, we considered only performance-based measures related to cognitive domains, thus excluding outcomes associated with behavioral, social, and emotional functioning, quality of life, and everyday cognitive functioning. This is because we were interested in examining only the efficacy of the programs on cognitive domains as assessed through performance-based measures, which constituted the specific targets of the interventions.

The literature search identified a total of 2,718 records on 31 January 2019. 637 records were collected from Scopus and 2,081 from PubMed databases. After the removal of duplicates ($n = 344$), titles of 2,374 records were screened. Based on the title, 2,272 records were excluded due to irrelevant content (e.g., adult populations and no cognitive/behavioral training) or format (e.g., case reports and narrative reviews). Of the remaining 102 records, the abstract screening led to 47 records considered to be eligible for full-text screening. Among the selected 47 records, 24 records were excluded due to irrelevant content or format, 9 records were reviews, and the remaining 14 records were studies eligible for this work. From the review screening, 4 reviews were considered to be not relevant, as they did not include technology-based training [19, 20] or were published in 2009-2010 [1, 18]. Thus, most recent reviews were preferred for study search [12, 14–17], after controlling that they included studies also reported in less recent reviews. 75 records were identified from the 5 pertinent reviews, of which 19 were duplicates. Of the 56 remaining records, 26 were considered to be eligible for full-text screening. Of these 26 records, 2 were excluded as the training was not home-based or required direct tutoring [37, 38] and 4 other records were removed as they applied the Amsterdam Memory and Attention Training for Children (AMAT-c [39–42]), which mostly proposes paper and pencil exercises [43]. Therefore, a total number of 19 records were obtained from the review screening. However, 6 records identified from review screening were duplicates of records identified from database searching. Therefore, after removing duplicates, a final number of 27 eligible studies was obtained from database search and review screening. Moreover, 4 records from software programs' website [44–47] were found. One more article meeting the eligibility criteria was found from expert network [48], leading to a total of 32 studies considered for this work. Figure 1 depicts the study inclusion procedure.

2.2. Meta-Analytic Exploration: Data Extraction and Analysis. For studies inserted in the meta-analytic exploration, sample size, mean, and standard deviation (SD) of the primary outcomes were extracted for both the intervention and the control group. If only error of the mean (SE) was provided, SD was calculated by applying the following formula $SD = SE \times \sqrt{n}$. For data presented graphically, we used the free online WebPlotDigitizer software to extract them from graphs (http://arohatgi.info/WebPlotDigitize). Moreover, first authors were contacted by e-mail if relevant data were not reported in the article.

Since all the studies delivering either cognitive or behavioral TP provided multiple outcome measures, we chose to adopt two distinct approaches to compute the observations to be inserted in the meta-analytic examination (see [49]).

With respect to cognitive TP, outcome measures of cognitive abilities extracted from the articles were classified into four main domains: (i) visuo-spatial skills, including visuo-spatial working memory and visuo-spatial attentional tasks; (ii) executive functions, including inhibition, planning, and cognitive flexibility tasks; (iii) math skills, including arithmetic operations and problems; and (iv) verbal skills, including verbal working memory, semantic/phonological processing, and reading tasks. A first meta-analytic model (model Cognitive A) included, for each study, an aggregated mean representing the mean value of the various outcomes related to all cognitive domains (namely, executive functioning, visual-spatial working memory, language, and math). In contrast, a second model (model Cognitive B) included, for each study, the mean of the outcomes of the cognitive domain that yielded the highest effect size. Indeed, since the primary outcome domain of studies was not always clearly identifiable, this alternative approach seems suitable if we assume that the outcome domain with the highest effect size may represent the cognitive function gaining the most beneficial effects from the TP, regardless of the authors' expectations (whether stated or not in the articles).

With respect to behavioral TP, a first model (model Behavioral A) included, for each study, an aggregated mean representing the mean value of the outcomes of the two assessed behavioral domains (namely, everyday executive functions and behavioral, social, and emotional functioning) combined together or the mean score of the only assessed behavioral domain. The mean score of the "behavioral, social, and emotional functioning" domain was calculated as the mean of the indexes/subscales of Child Behavior Checklist (CBCL), Home and Community Behavior Scale (HCSBS), and Behavioral and Emotional Rating Scale 2 (BERS 2). In case both parent- and child-compiled questionnaires were reported, we calculated an aggregated mean of the two scores for each index or subscale. The mean score of the "everyday executive function" domain was obtained by the score of the Global Executive Composite (GEC) scale of the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire, which was the only instrument adopted to evaluate this area throughout the included studies. In contrast, a second meta-analytic model (model Behavioral B) included, for each study, the mean of the behavioral domain that yielded the highest effect size, which was considered to be the area gaining the most beneficial effects from the TP.

Whenever a study reported results divided per subsamples of participants according to different characteristics (e.g., age range and severity of the diagnosis), the weighted mean $[(\mu_1 * n_1 + \mu_2 * n_2 + \cdots)/k]$ and pooled SD $[\sqrt{(SD_1{}^2 + SD_2{}^2 + \cdots + SD_n{}^2)/k}]$, where k = total number of participants per subsample, were calculated for each measure. Moreover, if a study reported both cognitive and behavioral measures, the outcome to be inserted in the model was chosen according to the focus of the intervention program. Therefore, an aggregate mean of all cognitive

Figure 1: Graphical depiction of the study inclusion procedure.

measures was calculated for studies applying a training with a focus on cognitive skills [35, 36, 46, 47, 50–52], whereas an aggregate mean of questionnaires and rating-scale scores was chosen for studies focusing on behavioral competences [23, 53–58]. For cognitive TP, performance-based measures were preferred over self-report scales, since only 4 out of the 7 included studies administered questionnaires. Moreover, adding questionnaire scores to performance-based measures would have introduced potential sources of heterogeneity. In a study on behavioral TP [57], three groups of participants were compared: a group performing traditional Teen Online Problem-Solving (TOPS-F), a group performing a modified version of the TOPS (TOPS-TO), and a control group assigned to Internet Resource Comparison (IRC). As the Authors reported that study participants were recruited as part of a randomized clinical trial between March 25, 2010, and August 6, 2014, and data on TOPS-F were reported in some previous studies [22, 23, 58], we decided to consider for the meta-analytic investigation only the comparison between TOPS-TO and IRC. Hedges's g was calculated for each study using the following formula:

$$g = \frac{(M1 - M2)}{(\mathrm{SD} * \mathrm{pooled})}. \quad (1)$$

Hedges's g is often referred to as a corrected effect size as compared to Cohen's d, as it corrects for a bias in the effect size due to the inclusion of studies with small samples [59]. The obtained effect sizes were then tested in random effects models. These models were preferred over a fixed-effect model due to the heterogeneous methodology applied across studies. Assessment of heterogeneity of the effect sizes was evaluated by calculating Q statistic, which indicates if the variance of the estimate effect sizes is greater than to be expected from sampling error, suggesting that the observed variance may be explained by other factors beside the intervention. Additionally, I^2 ratio, describing the percentage of variation across studies that is due to true heterogeneity rather than chance, was calculated to quantify and evaluate the consistency of the findings [60].

Finally, a nonparametric rank-order correlation between estimate effect sizes and sample sizes of the studies was calculated for the models Cognitive A and Behavioral A examining aggregate means of all outcome domains [61]. Indeed, a negative correlation between the two measures can be interpreted as a proxy for the presence of publication bias (for details see [62]).

A significance level of $p < .05$ was used for all analyses. Analyses were performed with Meta and Metafor software packages [63].

3. Results

3.1. Results from the Review Process

3.1.1. Cognitive Training Programs. 18 studies (see Table 1) investigated 7 different remote cognitive TP consisting of drill-based exercises aimed at stimulating different cognitive functions: TherapWii Protocol [34], Cogmed Working Memory Training [44–47, 50, 64], Lumosity Cognitive Training [21, 29], Captain's Log [35, 36, 65], Attention Improvement and Management (AIM) Program ([33, 66]), Brain Games Program [67, 68], and "Move it to improve it" (Mitii™) Protocol [51, 52]. Alongside exercises targeting cognitive functions, the AIM Program additionally proposed metacognitive strategy use, while the Mitii Protocol proposed web-based multimodal exercises, based on perceptual and motor abilities. The cognitive domains trained by the different programs were: attention, working memory, short- or long-term memory, language comprehension, executive functioning, processing speed, and math. All programs addressed specific cognitive functions, except the TherapWii Protocol, which was aimed at ameliorating the global physical, mental, and social functioning of the children and for which the intervention objectives in the various life domains were set on the basis of the areas in which the children exhibited an impairment. However, the majority of patients (47/50) recruited for receiving TherapWii Protocol [34] presented with problems on information processing and all of them received cognitive exercises. Moreover, in 3 studies [34–36], the TP could be performed not only in the ecological setting (home or school) but also in an individual rehabilitation setting with a therapist [34] or in a clinic without the presence of a therapist [35, 36]. The other programs were solely home-based.

Before training onset, patients usually received detailed instructions on how to perform exercises by a clinical researcher, usually in the hospital setting. In 2 studies [33, 66], the training protocol required patients to reach the clinical center to meet the therapist once a week to monitor performance and progress and to discuss the cognitive strategies to adopt in the tasks administered the following week. In 2 studies [35, 36], no therapist monitoring was provided, while in 2 studies [67, 68] participants received a calendar and a training schedule to self-monitor their own adherence and performance. In the remaining 12 studies, remote weekly contact (by phone or email) was provided by a therapist to monitor adherence and resolve possible problems encountered by participants.

The TP had a variable duration of 5-20 weeks, with a commitment varying from 2 to 6 days per week. In 2 studies [34, 65], the specific number of sessions per week was not defined, but a minimum weekly time engagement was required, which ranged from 50 minutes to 2 hours per week. All TP required only the use of a computer with Internet access, except the TherapWii Protocol, which required also the use of a Nintendo Wii, the Mitii Protocol, which required also the use of a Kinect to track gross motor or upper limb movements, and a version of Brain Games platform which was delivered through iPad. The difficulty of the tasks provided in the interventions was calibrated on patients' abilities in 13 out of 18 studies. Specifically, Brain Games, Cogmed Working Memory Training, Lumosity Cognitive Training, and Captain's Log were adaptive programs, automatically modifying the difficulty of the exercises based on the individual performance. Similarly, most cognitive exercises of the TherapWii Protocol [34] were adaptive. In contrast, the menu of drills and strategies of the AIM Program was

Table 1: Overview of the studies on Cognitive Training Programs.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Bangirana et al., [36]**	Pre/posttest design. Control group: passive control group.	$N = 65$ (E: 32, C: 33). Age: E: mean age = 10.09 years (SD = 2.64 years); C: mean age = 9.71 years (SD = 2.28 years). Diagnosis: cerebral malaria, at approximatively 45 months since injury.	Training: Captain's Log. Description: Captain's Log is a cognitive training aimed at stimulating attention, memory, visuomotor skills, and reason abilities. Fifteen of the 35 possible brain-training exercises of the program were chosen for this study. Training adaptation: the difficulty of exercises automatically increased based on the child's performance. Setting: clinic, home, or school. Duration: 16 sessions in 8 weeks. Frequency: twice a week. Therapist monitoring: not required.	(i) Working memory (ii) Psychomotor speed (iii) Visual attention (iv) Visual learning and memory (v) Spatial working memory and learning (vi) Visuomotor processing speed	*Cognitive functioning*: (i) "CogState" battery: working memory, detection, identification, card learning, maze learning, and maze chasing *Behavioral, social, and emotional functioning*: (i) CBCL (internalizing, externalizing, total problems)	Improvement in (i) Visuomotor processing speed (ii) Working memory (iii) Learning (iv) Internalizing problems (CBCL)
Bangirana et al., [35]**	Pre/posttest design. Control group: passive control group.	$N = 61$ (E: 28, C: 33). Age: 5-12 years. Diagnosis: severe malaria at 3 months since injury.	Training: Captain's Log. Description: Captain's Log is a cognitive training aimed at stimulating attention, memory, visuomotor skills, and reason abilities. Fifteen of the 35 possible brain-training exercises of the program were chosen for this study. Training adaptation: the difficulty of exercises automatically increased based on the child's performance. Setting: clinic, home, or school. Duration: 16 sessions in 8 weeks.	(i) Working memory (ii) Psychomotor speed (iii) Visual attention (iv) Visual learning and memory (v) Spatial working memory and learning (vi) Visuomotor processing speed	*Cognitive functioning*: (i) KABC-II: working memory, visual spatial ability, reasoning, learning, and planning (ii) TOVA *Academic functioning*: (i) WRAT-3: arithmetic, reading, and spelling *Behavioral, social, and emotional functioning*: (i) CBCL (internalizing, externalizing, total problems)	Improvement in (i) Learning mean score

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
			Frequency: twice a week. Therapist monitoring: not required.			
Hardy et al., [65]	Pre/posttest pilot design. Follow-up: at 3 months. Control group: no control group.	$N = 9$. Age: 10-17 years. Diagnosis: 6 BT, 3 ALL at 1-10 years since surgery and/or adjuvant therapies. Inclusion criteria based on cognitive functioning: (i) Presence of attention problems based on CPRS and WMI of WISC 4	Training: Captain's Log. Description: Captain's Log is a cognitive training aimed at stimulating attention, memory, visuomotor skills, and reason abilities. Training adaptation: the difficulty of exercises automatically increased based on the child's performance. Setting: home. Duration: 12 weeks. Frequency: at least 50 minutes of training per week. Therapist monitoring: weekly contact provided by a researcher for motivation and troubleshooting.	(i) Attention (ii) Concentration (iii) Memory (iv) Listening skills (v) Processing speed (vi) Self-control (vii) Hand-eye coordination (viii) Fundamental numerical concepts (ix) Basic problem solving/reasoning skills	*Cognitive functioning*: (i) WMI of WISC IV (digit-span, letter-number sequencing) *Behavioral, social, and emotional functioning*: (i) CPRS	Improvement in (i) WMI from baseline to 3-month follow-up (ii) Digit-span forward at post training (iii) Parent-reported attention across the 3 time points
Kesler et al., [21]	One-arm open trial pilot study. Pre/posttest design. Control group: no control group.	$N = 23$. Age: 7-19 years. Diagnosis: 14 ALL, 9 posterior fossa BT, at 6 months since surgery and/or adjuvant therapies. Inclusion criteria based on cognitive functioning: (i) Deficit in EF: two or more EF test scores > 1 SD under the normative mean or the FSIQ score	Training: Lumosity Cognitive Training. Description: Lumosity Cognitive Training is a brain training consisting of different games, each targeting one of the following cognitive domains: speed of processing, attention, memory, flexibility, and problem solving. Only those exercises addressing cognitive flexibility, attention, and working memory (available in 2007 at the beginning of the study) were chosen for the training used in this study.	(i) Cognitive flexibility (ii) Attention (iii) Working memory	*Cognitive functioning*: (i) WISC-IV or WAIS-III (ii) WRAML2 (list memory, picture memory) (iii) NEPSY II (animal sort for children of 7–16 years) (iv) D-KEFS (sorting test for children of 17–19 years) (v) WJ-III (cancellation test) (vi) MVPT-3 *Other measures*: (i) Neuroimaging data	Improvement in (i) Processing speed (ii) Cognitive flexibility (iii) Verbal and visual declarative memory (iv) Prefrontal cortex activation at post training, compared to baseline

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
			Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 40 sessions in 8 weeks. Frequency: 5 sessions/week, 20 minutes/session, 6 tasks/session. Therapist monitoring: weekly monitoring by research staff.			
de Kloet et al., [34]	Multicenter pre/posttest design. Control group: no control group.	$N = 50$. Age: 6-29 years. Diagnosis: 27 TBI, 23 ABI non-TBI, at 0-2 years since injury.	Training: TherapWii Protocol. Description: this program consists of different Nintendo Wii games, each one composed of several subgames. Training adaptation: the difficulty of the majority of games was automatically adjusted by the program, based on child performance. Setting: home, school, or clinic during an individual rehabilitation session. Duration: 12 weeks. Frequency: at least 20 minutes per week, for a maximum of 2 hours per week. Therapist monitoring: weekly contact provided by a therapist for motivation and troubleshooting.	(i) Working memory (ii) Attention (iii) Information processing (iv) Executive functioning (v) Visuospatial perception	*Cognitive functioning*: (i) ANT *Physical and/or behavioral, social, and emotional functioning*: (i) Time spent on physical activity: ad hoc Likert questionnaire (ii) Social participation: children's assessment of participation and enjoyment *Quality of life*: (i) Peds-QL	Improvement in (i) Alertness (ii) Attentional flexibility (iii) Visuospatial WM (iv) Motor tracking (v) Time on physical activities (vi) Quality of life regarding school and social participation

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Hardy et al. [47]**	Randomized study. Pre/posttest design. Follow-up: at 3 months Control group: active control group performing the *MegaMemo*, a computer-based program that consists of the same exercises as *Cogmed*^{RM}, but the level of difficulty does not increase.	$N = 20$ (9 BT; 11 ALL); (E: 13, C: 7). Age: 8-16 years. Diagnosis: BT and ALL, at 1 year since surgery and/or adjuvant therapies. Inclusion criteria based on cognitive functioning: (i) IQ > 70 (ii) Difficulties with attention and working memory, according to at least one of the following criteria: (1) T-score of inattention subscale of the CPRS-3 ≥ 75th percentile (2) Attention/concentration subscale or working memory indices of the WRAML2 > 1 DS below the mean (3) Attention/concentration subscale or working memory indices of the WRAML2 > 1 DS below the estimated IQ	Training: Cogmed Working Memory Training. Description: this program consists of exercises targeting verbal and visuospatial working memory. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 25 sessions in 5-8 weeks. Frequency: approximatively 3-5 sessions/week. Monitoring: weekly phone-based contact with a coach.	(i) Visuospatial and verbal working memory	*Cognitive functioning*: (i) WRAML2 (attention/concentration and working memory) *Everyday cognitive functioning*: (i) CPRS (inattention and learning problems scales)	Improvement in (i) Visuospatial working memory (i) Parent-rated learning problems
Sohlberg et al., [66]	Pilot study. Pre/posttest design. Control group: no control group.	$N = 11$. Age: 13-16 years. Diagnosis: TBI at > 12 months since injury. Inclusion criteria based on cognitive functioning: (i) Attention problems as defined by a frequency score of 2 or 3 on at least 4 out of the 9 items from the Attention Subscale of the Vanderbilt ADHD Diagnostic Parent Rating Scale	Training: Attention Improvement Management (AIM) training. Description: this training is a cognitive intervention aimed at improving attention and executive functions. The program combines computerized drill-based tasks and metacognitive strategy instruction. Training adaptation: difficulty of exercises was weekly adjusted by a therapist.	(i) Working memory (ii) Attention (inhibition, sustained, selective/focused attention) (iii) Executive functions (flexibility of thinking, inhibition, problem solving, planning, impulse control, concept formation, abstract thinking, and creativity in both verbal and spatial modalities)	*Cognitive functioning*: (i) TEA-Ch (the Score!, Walk/Do not Walk, Code Transmission, Sky Search) (ii) D-KEFS (Trail Making Test, Color-word Interference Test, and Tower Test) *Everyday cognitive functioning*: (i) BRIEF (GEC) *Other measures*: (i) GAS	Improvement in (i) Attention (ii) Parent reported executive functioning (iii) GAS

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
			Setting: home. Duration: 10 weeks; the treatment was extended by 1 week for each week that the child failed to complete at least 2 home practices. Frequency: 2-4 sessions/week, 20 minutes/session. Therapist monitoring: home practice sessions were tracked and monitored by a clinician via a USB drive. Weekly face-to-face meetings between the child and the research clinician were scheduled to review home practice and adjust exercise difficulty.			
Conklin et al., [46]**	Single-blind randomized controlled trial. Pre/posttest design. Control group: passive control group.	N = 68 (E: 34, C: 34). Age: 8-16 years. Diagnosis: ALL or BT (E: 34, 23 ALL +11 BT; C: 34, 24 ALL +10 BT), at least 1 year since surgery and/or adjuvant therapies. Exclusion criteria based on cognitive functioning: (i) IQ < 70	Training: Cogmed Working Memory Training. Description: this program consists of exercises targeting verbal and visuospatial working memory. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 25 sessions in 5-9 weeks. Frequency: approximatively 3-5 sessions/week, 30-45 minutes/session. Therapist monitoring: weekly phone-based contact with a coach.	(i) Verbal and visuospatial working memory	*Cognitive functioning*: (i) Abbreviated IQ of WASI (vocabulary, matrix reasoning) (ii) WISC IV (working memory, digit span forward, digit span backward, letter number sequencing, working memory index, spatial span forward, spatial span backward) (iii) CPT-II (omissions, hit reaction time) *Academic functioning*: (i) WJ-III (math fluency, reading fluency) *Everyday cognitive functioning*: (i) CPRS-3 (inattention, executive function) (ii) BRIEF (working	Improvement in (i) Working memory (spatial span backward) (ii) Attention (WISC-IV spatial span forward) (iii) Processing speed (CPT-II hit reaction time) (iv) Executive function (CPRS-3) (v) Functional magnetic resonance imaging revealed reduction in activation of left

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
					memory scale, metacognitive index) *Other measures*: (i) Neuroimaging data	lateral prefrontal and bilateral medial frontal areas.
Eve et al., [64]	Pre/post-test design. Follow-up: at 12 months. Control group: no control group.	$N = 7$ children (5 at follow-up). Age: 10-16 years. Diagnosis: arterial ischemic stroke, at 4-10 years since injury. Inclusion criteria based on cognitive functioning: (i) IQ scores within 2 SDs of the mean, as measured by the WASI or WISC 4	Training: Cogmed Working Memory Training. Description: this program consists of exercises targeting verbal and visuospatial working memory. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 25 sessions. Frequency: 5 sessions/week, about 30-40 minutes per day. Therapist monitoring: weekly phone-based contact with the coach.	(i) Verbal and visuospatial working memory	*Cognitive functioning*: (i) WMTB-C (digit recall, word list matching, word list recall and non-word list recall, block recall, listening recall, backward digit recall) (ii) Tea-Ch: (Sky Search, Score!, Score! Dual Task, Sky Search Dual Task, Walk/Do not Walk) *Academic functioning*: (i) WRAT-4 (mathematics)	Improvement in (i) Verbal working memory (not maintained at follow-up)
Phillips et al., [50]**	Double-blind, randomized, placebo-controlled trial. Pre/posttest design. Follow-up: at 3 months. Control group: control group performing non-adaptive tasks of a less demanding version of the Cogmed Working Memory Training.	$N = 27$ (E: 13, C: 14). Age: 8-15 years. Diagnosis: moderate to severe TBI, at >12 months since injury. Inclusion criteria based on cognitive functioning: (i) FSIQ > 80	Training: Cogmed Working Memory Training. Description: this program consists of exercises targeting verbal and visuospatial working memory. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 25 sessions.	(i) Visuospatial and verbal working memory	*Cognitive functioning*: (i) AWMA (digit recall, dot matrix) (ii) TEA-Ch (Sky Search Score, Sky Search DT, Creature Counting, Walk/Do not Walk) *Academic functioning*: (i) WIAT-II (word reading, reading comprehension, numerical operations)	Improvement in: (i) WM tasks (at post-training and follow-up) (ii) Reading comprehension (at post-training) (iii) Reading accuracy (at follow-up)

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
			Frequency: 5 sessions/week, about 30-40 minutes per day. Therapist monitoring: weekly phone-based contact with a coach.			
Sakzewski et al., [52]**	Randomized controlled trial. Pre/posttest design. Control group: control group undergoing usual care program.	$N = 58$ (E: 29, C: 29). Age: 8-16 years. Diagnosis: stroke ($N = 22$; E: 10, C: 12), TBI ($N = 19$, E: 11, C: 8), nontraumatic ABI ($N = 17$; E: 8, C: 9), at least 12 months since injury.	Training: "Move it to improve it" (Mitii™). Description: this training is a multimodal web-based rehabilitation intervention to improve occupational performance, visual perception, and upper limb speed. Training adaptation: the therapist weekly adjusted the exercise complexity based on child's performance and feedback from the child and family. Setting: home. Duration: 20 weeks. Frequency: 6 days/week, 30 minutes/day. Therapist monitoring: weekly remote monitoring provided by a therapist for motivation and troubleshooting.	(i) Physical domain (i.e., upper limb and gross motor abilities) (ii) Visuospatial perception (visual discrimination, spatial relations, visual memory, form constancy, sequential memory, figure ground, and visual closure)	*Motor functioning*: (i) AMPS (processing, motor skills) (ii) Jebsen-Taylor Test of Hand Function (iii) COPM (performance, satisfaction) (iv) AHA (school kids version) *Cognitive functioning*: (i) TVPS (overall standard score, discrimination, memory, spatial relations, sequential memory, figure ground, and closure)	Improvement: negligible changes
Treble-Barna et al., [33]	Open-label pilot study. Pre/posttest design. Control group: healthy control group ($n = 11$) receiving the same treatment.	$N = 24$ (E: 13, C: 11). Age: 9-15 years. Diagnosis: mild to severe TBI, at least 1 year since injury. Inclusion criteria based on cognitive functioning: (i) Evidence of behavioral attention problems (Vanderbilt ADHD Diagnostic Parent Rating Scale, Attention	Training: Attention Improvement and Management (AIM). Description: this training is a cognitive intervention aimed at improving attention and executive functions. The program combines computerized drill-based tasks and metacognitive strategy instruction.	(i) Working memory (ii) Attention (inhibition, sustained, selective/focused attention) (iii) Executive functions (flexibility of thinking, inhibition, problem solving, planning, impulse control, concept formation, abstract	*Cognitive functioning*: (i) TEA-Ch (the Score!, Walk/Do not Walk, Code Transmission, Sky Search) (ii) D-KEFS (Number-Letter Switching score from TMT, Inhibition/Switching score from CWIT, Total Achievement Score from the Tower Test)	Improvement in (i) Sustained attention (ii) Parent-reported EFs (iii) The majority of families also reported expected or more-than-expected

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
		Subscale: at least 4 items with a frequency score of 2 or 3)	Training adaptation: the difficulty of exercises was weekly adjusted by a therapist. Setting: home. Duration: 12 weeks. Frequency: 2-4 sessions/week. Therapist monitoring: weekly face-to-face meetings between the child and the research clinician were scheduled to review home practice and adjust exercise difficulty. Weekly face-to-face meetings between the child and the research clinician were scheduled to review home practice and adjust exercise difficulty.	thinking, and creativity in both verbal and spatial modalities)	*Everyday cognitive functioning*: (i) BRIEF (BRI, GEC, MI) *Other measures*: (i) GAS	personalized goal attainment
Carlson-Green et al., [44]	Pre/posttest design. Follow-up: at 6 months. Control group: no control group.	$N = 20$. Age: 8-18 years. Diagnosis: BT, at least 1 year since surgery and/or adjuvant therapies. Inclusion criteria based on cognitive functioning: (i) Working memory deficits (T − score ≥ 75th percentile on the attention scale of CBCL or T − score ≥ 75th percentile on the parent-rated working memory scale of BRIEF or WMI (WISC 4) > 1 SD below the mean) (ii) FSIQ ≥ 70	Training: Cogmed Working Memory Training. Description: this program consists of exercises addressing verbal and visuospatial working memory. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 35 sessions, in 8-12 weeks. Frequency: not reported. Therapist monitoring: intermittent emails from coaches.	(i) Visuospatial and verbal working memory	*Cognitive functioning*: (i) AWMA (at the baseline and immediately after training: digit recall, nonword recall, listening recall, backwards digit recall, dot matrix, mister X, mazes memory, and odd one out; at the baseline and at 6-month follow-up: word recall, digit recall, backwards digit recall, counting recall, dot matrix, mister X, and spatial recall) *Academic functioning*: (i) WJ-III (applied problems and passage, comprehension subtests)	Improvement in (i) Working memory at post training and at follow-up (i) Math achievement at follow-up (i) Executive functioning at follow-up

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
					Behavioral, social, and emotional functioning: (i) CBCL (internalizing scale, externalizing scale, total problems scale) *Everyday cognitive functioning*: (i) BRIEF, at baseline and 6-month assessment *Social functioning*: (i) ABAS-II, at baseline and 6-month follow-up *Other measures*: (i) NPS: index of a child's exposure to neurocognitive risk factors during cancer treatment	
Conklin et al., [45] (extension of Conklin et al., [46])	Single-blind randomized controlled trial. Pre/posttest design. Follow-up: at 6 months. Control group: passive control group.	$N = 68$ (E: 34, 23 ALL +11 BT; C: 34, 24 ALL +10 BT). Age: 8-16 years. Diagnosis: ALL or BT, at least 1 year since surgery and/or adjuvant therapies, without recurrence. Inclusion criteria based on cognitive functioning: (i) Digit span, letter-number sequencing, or spatial span performance (WISC-IV) > 1 SD below the normative mean (ii) IQ > 70 (WASI)	Training: Cogmed Working Memory Training. Description: this program consists of exercises targeting verbal and visuospatial working memory. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 25 sessions, in 5-9 weeks, 30-45 minutes/session. Frequency: not reported. Therapist monitoring: weekly phone-based contact with a coach.	(i) Verbal and visuospatial working memory	*Cognitive functioning*: (i) Abbreviated IQ of WASI (vocabulary+ matrix reasoning) (ii) WISC IV (working memory, digit span forward, digit span backward, letter number sequencing, working memory index, spatial span forward, spatial span backward) (iii) CPT-II (omissions, hit reaction time) *Academic functioning*: (i) WJ-III (math fluency, reading fluency) *Everyday cognitive functioning*: (i) CPRS-3 (inattention, executive function) (ii) BRIEF (working memory, metacognitive index) *Other measures*: (i) Neuroimaging data	Improvement: (i) Working memory and processing speed were unchanged from posttest to 6 month follow-up, indicating maintenance of training improvement.

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Piovesana et al., [51]**	Randomized waitlist controlled trial. Control group: waiting-list control group.	$N = 60$ (E: 30, C: 30). Age: 8-16 years. Diagnosis: mild, moderate, or severe ABI, at least 12 months since injury.	Training: "Move it to improve it" (Mitii™). Description: Internet-based, multimodal program aimed at exercising cognitive, visual perceptual, and physical (i.e., upper limb and gross motor) function areas. Training adaptation: weekly remote monitoring of a therapist to control performance and update the program difficulty. Setting: home. Duration: 20 weeks. Frequency: 6 days/week for 30 minutes. Therapist monitoring: regular contact via phone or email with participants and families by the therapist to provide feedback and support.	(i) Cognitive functions (ii) Visual-perceptual functions (iii) Physical functions (i.e., upper limb and gross motor abilities)	*Cognitive functioning*: (i) WISC 4 (digit span backward, symbol search, coding) (ii) CTMT (trail 2, 3, 4, 5) (iii) D-KEFS: color naming, word reading, inhibition scores from CWI (iv) TOL (v) TEA-Ch (Sky Search, Sky Search Dt Score) *Everyday cognitive functioning*: (i) BRIEF (BRI, MI, GEC)	Improvement: none
Verhelst et al., [68]	Pre/posttest design. Feasibility study with preliminary data on efficacy. Follow-up: at 6 months. Control group: no control group.	$N = 5$. Age: 16-17 years. Diagnosis: TBI, at least 1 year, but no more than 5 years since injury.	Training: Brain Games Program. Description: entertaining games aimed at stimulating working memory/executive functioning and attention. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 8 weeks. Frequency: 5 sessions/week. Therapist monitoring: none.	(i) Attention (ii) Working memory (iii) Processing speed	*Cognitive functioning*: (i) CPT III (ii) Flanker task (III) WISC III: digit span-forward, digit-span backward, digit symbol coding (iv) CANTAB: spatial span-forward and backward, stockings, intra-extradimensional set shift *Everyday cognitive functioning*: (i) BRIEF (BRI, MI, GEC)	Improvement: (i) Positive effect sizes were found for all measures, except the BRIEF (BRI).

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
			Participants received a calendar and a training schedule to self-monitor their own adherence and performance.			
Corti et al., [29]	Pre/posttest design. Feasibility study with preliminary data on efficacy. The main study on efficacy is a randomized controlled study, with a stepped-wedge design. Control group (in the main study): waiting-list group, performing the same cognitive training of the experimental group at a different time point.	$N = 32$. Age: 11-16 years. Diagnosis: 28 ABI (traumatic or nontraumatic) + 4 congenital brain damage, at least 1 year since injury.	Training: Lumosity Cognitive Training. Description: Lumosity Cognitive Training is a brain training consisting of different games, each targeting one of the following cognitive domains: speed of processing, attention, memory, cognitive flexibility, and problem solving. Five of the possible brain-training exercises of the program were chosen for this study. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 8 weeks. Frequency: 20 minutes/day, 5 days/week. Therapist monitoring: weekly remote monitoring provided by a researcher for motivation and troubleshooting.	(i) Memory (ii) Attention (iii) Executive functioning (iv) Processing speed (v) Arithmetic operations	*Cognitive functioning*: (i) Lumosity Performance Index (LPI): average performance across the different games	Improvement: (i) Increase in mean LPI between the first day and the last day of the training (Cohen's $d = 0.80$)

Table 1: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Vander Linden et al., [67] (extension of Verhelst et al., [68])	Pre/posttest design. Control group: passive control group.	$N = 32$ (E: 16, C: 16). Age: 11-17 years (mean: 15.8 years). Diagnosis: moderate to severe TBI (mean age at injury: 13.4 years, mean time since injury: 2.4 years).	Training: Brain Games Program. Description: entertaining games aimed at stimulating working memory/executive functioning and attention. Training adaptation: the difficulty of exercises was automatically and in real time adjusted by the program, based on the child's performance. Setting: home. Duration: 8 weeks. Frequency: 40 minutes/session, 5 days/week. Therapist monitoring: none. Participants received a calendar and a training schedule to self-monitor their own adherence and performance.	(i) Memory (verbal memory, visuospatial memory, and working memory) (ii) Attention (selective attention, sustained attention, and inhibition) (iii) Processing speed (iv) Nonverbal learning (v) Problem-solving and planning	*Cognitive functioning*: (i) Digit span (forward and backward) of WISC IV (ii) Spatial span (forward and backward) of WISC IV (iii) Flanker task (conflict cost) (iv) CPT III (reaction time) (v) Digit Symbol Substitution Test (vi) Stockings of Cambridge *Everyday cognitive functioning*: (i) BRIEF (GEC)	Improvement in (i) Digit span forward, Flanker test, CPT III, digit symbol substitution, stockings of Cambridge, and GEC at posttraining and at 6-month follow-up (ii) Digit span backwards at 6-month follow-up (iii) Executive functions in daily living (BRIEF) for patients without diffuse-axonal-injuries in deep brain nuclei

Note: **study included in the meta-analytic exploration. Inclusion criteria indicated in the table only refers to those reported in the studies with respect to cognitive functioning. Other inclusion criteria based on demographic factors were omitted. ABAS-II: Adaptive Behavior Assessment System, 2nd Edition; ABI: acquired brain injury; AHA: The Assisting Hand Assessment; AIS: arterial ischemic stroke; ALL: acute lymphoblastic leukemia; AMPS: Assessment of Motor and Process Skills; ANT: Amsterdamse Neuropsychologische Taken Programme; AWMA: Automated WM Assessment; BRI: Behavioral Regulation Index; BT: brain tumor; C: control group; CANTAB: Cambridge Automated Neuropsychological Test Battery; CBCL: Child Behavioral Checklist; COPM: Canadian Occupational Performance Measure; CPRS: Conners' Parent Rating Scale; CPT: Continuous Performance Test; CTMT: Comprehensive Trail Making Test; CWIT: Color-Word Interference Test; DKEFS: Delis Kaplan Executive System; DSM-IV: Diagnostic and Statistical manual, 4th edition; E: experimental group; EF: executive functions; FSIQ: Full Scale Intelligence Quotient; GAS: Goal Attainment Scale; GCS: Glasgow Coma Scale; GEC: Global Executive Composite; KABC-II: Kaufman Assessment Battery for Children, 2nd edition; GMFCS: Gross Motor Function Classification Scale; MI: Metacognitive Index; MVPT-3: Motor Free Test of Visual Perception, 3rd Edition; NPS: Neurological Predictor Scale; NEPSY II: Developmental NEuroPSYchological Assessment; PRI: Perceptual Reasoning Index; PSI: Processing Speed Index; SD: standard deviation; TEA-Ch: Test of Everyday Attention for Children; TMT: The Trail Making Test; TOVA: Test of Variables of Attention; TT: Tower Test; TVPS: Test of Visual Perceptual Skills; WAIS-III: Wechsler Intelligence Scale, 3rd edition; WASI: Wechsler Abbreviated Scale of Intelligence; WISC IV: Wechsler Intelligence Scale for Children, 4th edition; VCI: Verbal Comprehension Index; WIAT-II: Wechsler Individual Achievement Tests, 2nd Edition; WJ-III: Woodcock-Johnson 3rd Edition; WM: working memory; WMI: Working Memory Index; WMTB-C: Working Memory Test Battery for Children; WRAML2: Wide Range Assessment of Learning and Memory, 2nd Edition; WRAT-3: Wide Range Achievement Test, 3rd edition; WRAT-4: Wide Ranging Achievement Test, 4th edition.

initially defined by a clinician on the basis of neuropsychological testing, parent and child reports, and progressively updated by a therapist during training in accordance with changes in performance [33, 66]. With respect to the Mitii Protocol, the complexity of exercises was adjusted weekly by a trainer based on performance and comments provided by the child and family [51, 52].

With respect to study methodology, the sample size of studies varied between $n = 5$ and $n = 68$, with 5 studies including < 20 total participants [33, 64–66, 68]. Nine studies [29, 35, 36, 45–47, 50–52] had an active or a passive control group of children with ABI performing low-demanding TP or no training, respectively. In contrast, a study [33] had a control group of healthy children performing the same experimental training. Participants had ABI of both traumatic (TBI) and nontraumatic nature (e.g., stroke, brain tumor, and cancer-related treatments). One study [29] included also patients with congenital brain damage ($n = 4$).

Regarding inclusion criteria, studies were generally conducted on patients without sensory or motor deficits that could interfere with participation in the TP. Moreover, some studies [44–47, 50, 64] established a criterion based on IQ, excluding patients with clinically impaired or borderline intellectual functioning. Some other studies [34, 51, 52] excluded individuals with severe cognitive impairment, but without declaring a specific IQ threshold. In contrast, another study [29] included patients with very low IQ to test the feasibility of the selected TP among the general population of children with brain damage, who displays heterogeneous cognitive functioning. Moreover, 5 studies [21, 33, 44, 47, 65, 66] reported as inclusion criterion the presence of specific cognitive deficits in attention and/or memory abilities or executive functions, as measured through neuropsychological tests and/or parents' reports.

The measures used to test cognitive outcomes were all standardized in 16 out 18 studies. In contrast, in the study of Corti et al. [29], which was aimed at assessing feasibility as primary objective, only preliminary results on training effectiveness were indicated. These results were based on a nonstandardized index directly supplied by the cognitive TP and indicating the average change in performance between the first and the last training day, which could be considered as a near-transfer measure. Linden and colleagues [67] used both standardized tests and nonstandardized computerized tasks. Two studies out of 18 [51, 52] reported no improvement. In the other 16 studies, improvements after training were found both in near-transfer and/or far-transfer measures (e.g., academic achievement and everyday functioning), at least at post-training assessment.

3.1.2. Behavioral Training Programs. With respect to technology-based TP aimed at improving behavioral issues, a series of 14 studies conducted between 2005 and 2018 by the same research group in the USA were included in this work (see Table 2). 12 studies investigated the efficacy of family web-based interventions aimed at improving executive, behavioral, and social functioning of children with TBI. In particular, 6 studies focused on the Counselor-Assisted Problem Solving (CAPS) intervention [53, 54, 56, 69–71], 2 studies on the Online Family Problem-Solving (OFPS) program [55, 72], and 4 studies on the Teen Online Problem-Solving (TOPS) intervention [22, 23, 57, 58]. The remaining 2 studies focused on the Social Participation and Navigation (SPAN) intervention [48, 73], a training aimed at improving social abilities in children with TBI or brain tumor.

The CAPS, OFS, and TOPS programs consisted of self-guided, online sessions performed by the child and his/her family at home and of Skype videoconferences with a coach with expertise in cognitive-behavioral therapy. Such videoconferences were included with the purpose of reviewing the exercises completed by participants and providing feedback on the implementation of the problem-solving process in real life. Specifically, the training was composed of 8-10 core sessions focusing on executive functions, social skills, injury-related issues, and other eventual supplemental sessions. Participants were advised to perform supplemental sessions only if their specific content was evaluated potentially beneficial for the ongoing problems of the child and/or the family at the baseline assessment.

The SPAN program, together with online didactic sessions, included a dedicated iPhone application to set children social goals and weekly videoconferencing sessions (via Skype) with a trained college-student coach. The introduction of a peer as a coach instead of the therapist was motivated by the fact that the impact of peers becomes increasingly relevant through adolescence [48, 73].

In some studies [22, 23, 55, 58, 72], meetings with the coach [48, 73] were scheduled every 1-2 weeks, whereas in other studies [53, 54, 56, 57, 69–71] they were scheduled every 2-4 weeks. The CAPS, OFS, and TOPS program duration could approximatively range from 6 months to 8 months, based on the total number of sessions assigned to participants. The SPAN program duration ranged from 4 weeks [73] to 10 weeks [48].

With respect to study methodology, the sample size of studies varied between $n = 4$ and $n = 132$, with 4 studies including < 20 families [22, 48, 72, 73]. In the early studies, participants were aged between 5 and 16 years [55, 72], while in the subsequent studies they were only adolescents [22, 23, 48, 53, 54, 56–58, 69–71, 73]. Only one study extended to 22 years the age range of participants [48]. In all studies, children were included if they sustained a moderate-to-severe TBI about 1-24 months before the intervention. Only a study [48] included also participants with a diagnosis of brain tumor.

In the majority of the studies, children who experienced blunt trauma or history of abuse and had familiarity for psychiatric hospitalization were excluded. In those studies that were conducted between 2013 and 2016 [53, 54, 56, 69, 71], the presence of intellectual disability before the injury was set as a further exclusion criterion.

Eleven out of the 14 studies included in this work were randomized controlled trials. In 10 studies [23, 25, 53–56, 58, 69–71], the children and their families could be randomly assigned to one of the TP described above (CAPS, OFPS, or

Table 2: Overview of the studies on Behavioral Training Programs.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Wade et al., [72]	Pilot study. Pre/posttest design.	$N = 6$. Age: 5-16 years. Diagnosis: mild to severe TBI at more than 15 months since injury.	Training: OFPS. Setting: home. Duration: 6 months for the 8 core sessions +4 supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Everyday executive functions*: (i) BRIEF (parent report): GEC *Behavioral, social, and emotional functioning*: (i) HCSBS (parent report): antisocial behavior subscale (ii) CDI (self-report)	Reduction of antisocial behaviors.
Wade et al., [55]**	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to IRC.	$N = 39$ (E: 20, C: 19). Age: 5-16 years. Diagnosis: mild to severe TBI at 1-24 months since injury.	Training: OFPS. Setting: home. Duration: 6 months for the 8 core sessions +6 eventual supplemental sessions. Therapist monitoring: Skype sessions with a therapist every 1-2 weeks.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent report): externalizing, internalizing, and total problems (ii) HCSBS (parent report): peer total, self-management/ compliance, total scale	Improvement in self-control and compliance with parents.
Wade et al., [22]	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to the same treatment program (TOPS), but without audio.	$N = 9$ (E: 5, C: 4). Age: 11-18 years. Diagnosis: mild to severe TBI at <24 months since injury.	Training: TOPS with audio. Setting: home. Duration: 6 months for the 10 core sessions +4 eventual supplemental sessions. Therapist monitoring: Skype sessions with a therapist every 1-2 weeks.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Everyday executive functions*: (i) BRIEF (parent report): GEC *Behavioral, social, and emotional functioning*: (i) CBCL (parent report): externalizing, internalizing, and total problems (ii) CDI (self-report)	Reduction of self-reported depression symptoms and of internalizing symptoms in children of both groups. Adolescent assigned to the audio condition showed a greater improvement in internalizing symptoms.
Wade et al., [23]**	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to IRC.	$N = 35$ (E: 16; C: 19). Age: 11-18 years. Diagnosis: mild to severe TBI at <18 months since injury.	Training: TOPS. Setting: home. Duration: 6 months for the 10 core sessions +4 eventual supplemental sessions. Therapist monitoring: Skype sessions with a therapist every 1-2 weeks.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Everyday executive functions*: (i) BRIEF (parent and youth self-report): GEC, BRI, MI	Significant improvement in executive function behaviors in teens with severe TBI.

Table 2: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Wade et al., [58]**	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to IRC.	$N = 35$ (E: 16, C: 19). Age: 11-18. Diagnosis: mild to severe TBI at 3-19 months since injury.	Training: TOPS. Setting: home. Duration: 6 months for the 10 core sessions +4 eventual supplemental sessions. Therapist monitoring: Skype sessions with a therapist every 1-2 weeks.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent and youth self-report): externalizing and internalizing problems	Reduction of parent-teen conflict. Reduction of internalizing symptoms among adolescents with severe TBI.
Kurowski et al., [53]**	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to IRC.	$N = 110$ (E: 57, C: 63). Age: 12-17 years. Diagnosis: mild to severe TBI at 1-6 months since injury.	Training: CAPS. Setting: home. Duration: 6 months for the 10 core sessions +6 eventual supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist in months 1-3; be-weekly Skype sessions in months 4-6.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Everyday executive functions*: (i) BRIEF (parent report): GEC, BRI, MI	Improvement in executive function behaviors observed in older teens.
Kurowski et al., [69] (extension of Kurowski et al., [53])	Randomized controlled study. Pre/posttest design. Follow-up: at 12 and 18 months. Control group: active control group, assigned to IRC.	$N = 131$ (E: 65, C: 66). Age: 12-17 years. Diagnosis: mild to severe TBI at 1-6 months since injury.	Training: CAPS. Setting: home. Duration: 6 months, for the 10 core sessions +6 eventual supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist in months 1-3; be-weekly Skype sessions in months 4-6.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Everyday executive functions*: (i) BRIEF (parent report): GEC, BRI, MI	Improvement in executive function behaviors observed in older teens both at 12- and 18-month follow-up.
Wade et al., [56]**	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to IRC.	$N = 131$ (E: 65, C: 66). Age: 12-17 years. Diagnosis: mild to severe TBI at 1-6 months since injury.	Training: CAPS. Setting: home. Duration: 6 months, for the 10 core sessions +6 eventual supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist in months 1-3; be-weekly Skype sessions in months 4-6.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent report): externalizing and internalizing problems+aggressive, attention, ADHD, and conduct scales	Improvement in externalizing symptoms in older teens.

Table 2: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Wade et al., [70] (extension of Kurowski et al., 2011, [53]; Wade et al., [56])	Randomized controlled study. Pre/posttest design. Follow-up: at 12 and 18 months. Control group: active control group, assigned to IRC.	$N = 131$ (E: 65, C: 66). Age: 12-17 years. Diagnosis: mild to severe TBI at <7 months since injury.	Training: CAPS. Setting: home. Duration: 6 months, for the 10 core sessions +6 eventual supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist in months 1-3; be-weekly Skype sessions in months 4-6.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CAFAS (parent report): total scale	Improvement in everyday functioning, especially in families of lower socioeconomic status.
Wade et al., [71] (extension of Wade et al., [56])	Randomized controlled study. Pre/posttest design. Follow-up: at 12 and 18 months. Control group: active control group, assigned to IRC.	$N = 132$ (E: 65, C: 67). Age: 12-17 years. Diagnosis: mild to severe TBI at 1-6 months since injury.	Training: CAPS. Setting: home. Duration: 6 months, for the 10 core sessions +6 eventual supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist in months 1-3; be-weekly Skype sessions in months 4-6.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent report): externalizing and internalizing problems	Improvement in behavior problems in older adolescents and those with pretreatment symptoms.
Tlustos et al., [54]**	Randomized controlled study. Pre/posttest design. Control group: active control group, assigned to IRC.	$N = 132$ (E: 65, C: 67). Age: 11-18 years. Diagnosis: mild to severe TBI at 1-6 months since injury.	Training: CAPS. Setting: home. Duration: 6 months, for the 10 core sessions +6 eventual supplemental sessions. Therapist monitoring: weekly Skype sessions with a therapist in months 1-3; be-weekly Skype sessions in months 4-6.	(i) Everyday executive functions (ii) Behavioral, social, and emotional functioning	*Everyday executive functions*: (i) BRIEF (parent and youth self-report): GEC *Behavioral, social, and emotional functioning*: (i) HCSBS (parent report): social competence subscale (ii) CBCL (parent report): social competence subscale (iii) BERS 2 (parent report): social competence subscale	Improvement in social competence. Greater improvement in younger teens with moderate TBI.
Narad et al., [73]	Pilot study. Pre/posttest design. Control group: no control group.	$N = 4$. Age: 14-17 years. Diagnosis: mild to severe TBI during childhood (mean age at injury: 7.27 years, mean time since injury: 8.46 years).	Training: SPAN. Setting: home. Duration: 4 weeks. Therapist monitoring: weekly videoconferencing sessions via Skype with a trained college-student coach.	(i) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent and youth self-report): social competence, social problems and total problems scales	Improvement in social participation. Medium to large effect sizes were found for adolescent self-reported measures. Negligible effects were observed for parent-reported measures.

Table 2: Continued.

Study	Research design	Sample	Treatment characteristics	Treatment domain(s)	Outcome measures	Main findings
Wade et al., [48]	Pilot study. Pre/posttest design. Control group: no control group.	*N* = 15. Age: 14-22 years. Diagnosis: 9 TBI (moderate or severe); 6 BT (at least 2 years out from treatment completion or from diagnosis if treatment was not indicated).	Training: SPAN. Setting: home. Duration: 10 weeks. Monitoring: weekly videoconferencing sessions via Skype with a coach for 30-60 minutes.	(i) Behavioral, social, and emotional functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent and youth self-report): internalizing, externalizing, and total problems scales+social problems and social competence scales	Improvement in parent reported frequency of social participation and total, internalizing, and externalizing problems; improvement in teen-reported confidence ability to participate and develop social participation goals and plans.
Wade et al., [57]**	Randomized controlled study. Pre/posttest design. Control group: two versions of the TOPS program (TOPS-F and TOPS-TO) were compared with an active control group, assigned to IRC.	*N* = E1 (TOPS-TO): 51; E2 (TOPS-F): 49, C: 52. Age: 11-18 years. Diagnosis: mild to severe TBI at <18 months since injury.	Training: TOPS-TO or TOPS-F. Setting: home. 6 months for the 10 core sessions +4 eventual supplemental sessions. Monitoring: Skype sessions with a therapist every 1-2 weeks.	(i) Everyday executive functions (ii) Behavioral functioning	*Behavioral, social, and emotional functioning*: (i) CBCL (parent and youth self-report): externalizing problems *Everyday executive functions:* (i) BRIEF (parent and youth self-report): GEC	Improvement in executive functioning in the TOPS-F group, as compared to the TOPS-TO group. Differences between the TOPS-F and IRC groups approached significance. Maternal education and parental stress levels moderated improvements.

Note: ** study included in the meta-analytic exploration. Outcomes reported in the table refer only to children. ADHD: attention deficit and hyperactivity disorder; BERS 2: Behavioral and Emotional Rating Scale 2; BRI: Behavioral Regulation Index; BRIEF: Behavior Rating Inventory of Executive Function; BT: brain tumor; C: control group; CAFAS: Child and Adolescent Functional Assessment Scale; CAPS: Counselor-Assisted Problem Solving; CBCL: Child Behavior Checklist; CDI: Children's Depression Inventory; E: experimental group; GEC: Global Executive Composite; HCSBS: Home and Community Behavior Scale; IRC: Internet Resource Comparison; MI: Metacognition Index; OFPS: Online Family Problem-Solving; SES: socioeconomic status; SPAN: Social Participation and Navigation; TBI: traumatic brain injury; TOPS: Teen Online Problem-Solving; TOPS-F: Teen Online Problem-Solving-Family; TOPS-TO: Teen Online Problem-Solving-Teen Only; WEQ: Website Evaluation Questionnaire.

Figure 2: Forest plots showing the number of participants per group, effect size estimates (Hedges's g), and 95% confidence interval of each study, comparing cognitive training outcomes with control condition's outcomes. Model Cognitive A depicts the meta-analytic model that considers, for each study, a combined mean value representing the mean value of multiple outcomes relative to all cognitive domains. Model Cognitive B depicts the meta-analytic model that considers, for each study, the highest outcome domain. Note: VSP = visuo-spatial skills; MTH = math; VRB = verbal; EF = executive functioning.

TOPS) or to an Internet Resource Comparison (IRC), used as a control condition activity. In one study [22], the control group received the TOPS intervention void of audio content.

The efficacy of the interventions was assessed through parent-report or self-report questionnaires evaluating everyday executive functions and behavioral, social, and emotional functioning. With respect to outcomes on children, all studies reported positive gains from the interventions in the various domains assessed. Results also revealed that these treatments reduced parent-teen conflicts.

3.2. Results from the Meta-Analytic Exploration. The first random effects model on cognitive TP (Cognitive A), including the aggregate means of all reported outcomes of the 7 eligible studies, yielded a nonsignificant estimated effect size of -.02, 95%CI = −0.45; 0.42, $Z = -0.08$, $p = .94$ (Figure 2). Total heterogeneity of the effect sizes was significant as indicated by $Q = 23.32$, $p < .001$, and $I^2 = 74.3\%$ (45.1%-87.9%), revealing the presence of high methodological and/or statistical heterogeneity between studies.

The model Cognitive B, including the measures returning the highest effect sizes in cognitive training studies, yielded a significant estimated effect size of .61, 95%CI = 0.07; 1.16, $Z = 2.19$, $p = .03$ (Figure 2). Total heterogeneity of the effect sizes was significant, as indicated by $Q = 34.7$, $p < .0001$, and $I^2 = 82.7\%$ (65.7%-91.3%), confirming the presence of high methodological and/or statistical heterogeneity between studies.

Regarding the behavioral TP, model Behavioral A, including the aggregate means of all reported outcomes, yielded a significant effect size of .38, 95%CI = 0.03-0.72, $Z = 2.15$, $p = .03$ (Figure 3). High heterogeneity was detected by $Q = 20.95$, $p < .002$, and $I^2 = 71.4\%$ (37.8%-86.8%).

The last model, Behavioral B (Figure 3), including the highest outcome of each of the 7 behavioral training studies, yielded a significant effect size of .39, 95%CI = 0.07-0.73, $Z = 2.35$, $p = .02$. High heterogeneity was detected by $Q = 19.87$, $p < .003$, and $I^2 = 69.8\%$ (33.7%-86.2%).

The subgroup analysis conducted on the model Cognitive B on the outcomes associated with the greatest improvement showed a significant effect size of .37, 95%CI = 0.06-0.69, $Z = 2.34$, $p = .02$, for the subgroup of measures assessing visuo-spatial skills ($k = 4$) (the remaining three outcomes referred each one to a different cognitive function—i.e., executive function, math, and verbal skills), accompanied by a sensible reduction in total heterogeneity as detected by both $Q = 1.19$, $p = .76$, and $I^2 = 0.0\%$ (0.0%; 61.5%).

Lastly, the nonparametric rank-order correlation between the effect size estimates and sample size across studies was nonsignificant for both model Cognitive A ($r = -.09$, $p = .84$) and model Behavioral A ($r = -.39$, $p = .39$), showing no clear evidence for publication bias.

3.3. Risk of Bias. In order to assess the validity and evaluate potential methodological problems of the included studies, two researchers (VO and EF) screened the articles on cognitive TP and two researchers (CC and CO) screened the articles on behavioral TP. The evaluation of risk of bias in this work was applied to all included studies, not only to clinical trials, in order to provide a detailed overview of methodological study characteristics. For this purpose, the researchers considered the domains included in Risk of Bias Tool of The Cochrane Collaboration [60]. This tool provides a guide to assess methodological quality of clinical and research trials according to the following five domains: (i) selection bias, which refers to the method of allocation to treatment condition, considering both sequence of randomization (unpredictable or not) and adequate concealment of the allocation sequence from those involved in the enrollment and assignment of participants; (ii) performance bias (potential cause of expectation and placebo-induced effects), deriving from unsuccessful blinding of participants and personnel to treatment allocation; (iii) detection bias, deriving from unsuccessful blinding of outcome assessors to participants' treatment allocation that may influence data collection and analysis; (iv) attrition bias, usually detected in the presence of a not justified high proportion of missing outcomes due to participant drop-out (attrition) during the study or exclusions from the analysis, causing a possible observed biased effect estimate. Attrition could be due to participants' withdrawal, missing of a scheduled appointment at which outcomes should have been measured, unsuccessful data collection

Figure 3: Forest plots showing the number of participants per group, effect size estimates (Hedges's g), and 95% confidence interval of each study, comparing behavioral training outcomes with control condition's outcomes. Model Behavioral A depicts the meta-analytic model that considers, for each study, an aggregated mean representing the mean value of the various outcomes relative to all behavioral domains. Model Behavioral B depicts the meta-analytic model that considers, for each study, the highest outcome domain. Note: BSEF = behavioral, social, and emotional functioning; EEF = everyday executive functioning.

during an appointment, failing to complete questionnaires, loss to follow-up associated with the fact that participants cannot be located, follow-up ceasing by researchers, and loss of data and records; and (v) reporting bias, indicating the risk that non-significant results may be withheld from publication due to selective omission of outcomes from reports, selective choice of data for an outcome, selective reporting of analyses using the same data, selective reporting of subsets of the data, and selective underreporting of data. The absence of a registered protocol or the presence of a registered protocol without an exact description of instruments used to assess outcomes could represent a potential risk of reporting bias. The risk associated with each assessed domain was judged as low, high, or unclear. In case that such an evaluation was not applicable, this was indicated. The researchers provided judgements on risks of bias for all studies independently and then reached a final agreement in case of discrepancies. Results are summarized in Table 3.

With respect to cognitive TP, selection bias associated with random sequence was judged low for 52.9% of studies, while the other half had an experimental design that could not allow the assessment of sampling method. Selection bias associated with allocation to treatment methods was judged low for 16.6% of the studies, high for 11.1%, and unclear for 22.2%. For the remaining studies (50.1%), this criterion was not assessable. Performance bias associated with blinding of participants and personnel procedure was associated with low risk of bias for 22.2% of the included records, whereas 16.6% was judged at high risk of bias and 11.1% was defined as at unclear risk of bias. For the remaining 50.1% of studies, this criterion was not assessable. Detection bias associated with blinding of assessor procedure was associated with low risk of bias in 44.6% of the studies, high risk of bias in 27.7%, and unclear risk of bias in 27.7%. Attrition bias associated with incomplete outcome data was associated with low risk of bias in 66.7% of the studies, with the remaining 33.3% being associated with high risk. Reporting bias associated with selective reporting was associated with unclear risk of bias in 100.0% of the studies.

Considering behavioral TP, selection bias associated with random sequence was judged low for 71.4% and unclear for 7.1% of the studies, while for the remaining 21.4% it was not assessable. Selection bias associated with allocation to treatment methods was judged low for 35.7% of the studies, high for 23.5%, and unclear for 14.3%. For the remaining 21.4%, this criterion was not applicable. Performance bias associated with blinding of participants and personnel procedure was associated with high risk of bias for 78.6% of the included records, whereas for the remaining 21.4% this criterion was not applicable. Detection bias associated with blinding of assessor procedure was associated with low risk of bias in 42.9% of the studies, high in 28.6%, and unclear in 28.6%. Attrition bias associated with incomplete outcome data was associated with low risk of bias for 21.4% of the studies, high risk for 21.4%, and unclear for 57.2%. Reporting bias associated with selective reporting was associated with high risk of bias for 14.3% of the studies and unclear for the remaining 85.7%.

4. Discussion

This review described 32 technology-based TP (training programs) for pediatric patients with different types of ABI delivered in the ecological setting, of which 18 were cognitive TP and 14 behavioral TP. A meta-analytic exploration was also conducted on a subsample of 14 studies applying a control-group design (7 cognitive TP and 7 behavioral TP), in order to provide an estimation of the overall mean effect of the eligible studies. The presence of a control group of participants should be considered as an essential methodological element in studies investigating treatment efficacy [32], as it allows controlling for the effects of spontaneous development in pediatric age and possible expectation bias. The picture offered by this review indicates that, nowadays, about half of the studies on remote TP addressing cognitive functions for pediatric ABI lacks a control on these aspects. With respect to behavioral TP, most of the studies included a control group, thus being in line with the methodological recommendations of evidence-based research.

Based on the review process, 16 out of the 18 studies on cognitive TP were found to be effective in improving cognitive outcomes immediately after training, on both near-

Table 3: Risk of bias summary.

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	Random sequence	Allocation	Blinding of participants and personnel	Blinding of assessors	Incomplete outcome data	Selective reporting
Cognitive Training Programs						
Bangirana et al., [36]**	+	—	—	—	+	?
Bangirana et al., [35]**	+	?	—	—	+	?
Carlson-Green et al., [44]	/	/	/	—	+	?
Conklin et al., [46]**	+	?	?	+	—	?
Conklin et al., [45]	+	?	?	+	+	?
Corti et al., [29]	+	—	+	+	+	?
de Kloet, et al., [34]	/	/	/	?	+	?
Eve, et al., [64]	/	/	/	?	—	?
Hardy et al., [65]	/	/	/	?	—	?
Hardy et al., [47]**	+	?	+	+	—	?
Kesler et al., [21]	/	/	/	+	+	?
Phillips et al., [50]**	+	+	+	+	+	?
Piovesana et al., [51]**	+	+	+	?	—	?
Sakzewski et al., [52]**	+	+	—	+	+	?
Sohlberg et al., [66]	/	/	/	—	—	?
Treble-Barna et al., [33]	/	/	/	—	+	?
Vander Linden et al., [14]	/	/	?	+	+	?
Verhelst et al., [68]	/	/	/	?	+	?
Behavioral Training Programs						
Kurowski et al., [53]**	+	+	—	+	?	?
Kurowski et al., [69]	+	+	—	+	?	?
Narad et al., [73]	/	/	/	?	+	?
Tlustos et al., [54]**	?	?	—	+	?	?
Wade et al., [72]	/	/	/	?	+	?
Wade et al., [55]**	+	—	—	—	—	?
Wade et al., [22]	+	—	—	—	+	—
Wade et al., [23]**	+	—	—	—	—	?
Wade et al., [58]**	+	—	—	—	—	—
Wade et al., [56]**	+	+	—	+	?	?
Wade et al., [70]	+	+	—	+	?	?
Wade et al., [71]	+	+	—	+	?	?
Wade et al., [48]	/	/	/	?	?	?
Wade et al., [57] **	+	?	—	?	?	?

Symbol legend: +: low risk of bias; -: high risk of bias; /: not applicable (e.g., allocation to treatments in a study with no control group); ?: unclear risk of bias. Asterisks ** mark studies included in the meta-analytic exploration.

and far-transfer measures. Moreover, 8 out of the 12 studies on cognitive TP that considered also outcomes on functioning in daily life found positive gains. This would suggest that computer-based interventions offering drill-based exercises delivered in an ecological setting are effective at improving cognitive abilities and adjustment in children with ABI. Nevertheless, data of our meta-analytic exploration seem to suggest that cognitive TP are unlikely to have a positive impact on different cognitive domains, suggesting limited generalized effects. Indeed, the meta-analysis conducted on the combined mean of all cognitive outcomes of studies showed no effect (model Cognitive 1). In contrast, the meta-analytic model on the cognitive domain associated with the highest improvement for each study (model Cognitive 2) yielded an effect of moderate level ($g = 0.61$), according to criteria taken from previous literature [74]. This points to the efficacy of cognitive TP in producing benefits limited to specific cognitive domains, probably those that are mostly stimulated by training tasks. Nevertheless, a high level of heterogeneity ($I^2 = 83.2\%$) was detected. Such a high heterogeneity could be related to various factors associated with characteristics of the samples (e.g., age range, diagnosis subcategory, and

time from injury) or of the TP (e.g., focus, duration, adaptation of exercise difficulty, and trained cognitive domains). An additional explorative analysis, performed to evaluate potential differences in TP effects across cognitive domains, highlighted that measures assessing visuo-spatial skills, which represented the highest outcome domain in 4 out of 7 studies, yielded a small, yet significant estimate effect size. This result was accompanied by a low level of heterogeneity, thus indicating that it could constitute a more precise estimation of cognitive TP effects. The improvement in visuo-spatial skills may be due to an intensive stimulation of visuo-spatial processes throughout all TP tasks, which is in accordance with data from previous research indicating that video- and computer-game playing stimulate visuo-spatial abilities, even after a limited training duration [75–77]. For outcomes related to executive functions, verbal and math skills, we could not evaluate the overall training effects, as only one study per domain was available.

On a related note, it is important to stress that the limited amount of studies on cognitive TP eligible for inclusion in the meta-analysis did not allow us to examine in more details the impact of factors that may explain the variability emerged across studies (e.g., training adaptation, duration, match between training focus and primary study outcome). Future research should explore these aspects to identify and weigh their contribution to the success of interventions.

With respect to behavioral interventions, 14 studies from the same team of researchers in the USA were included in this work. Based on the review process, results on these programs are encouraging, as all studies found improvements in everyday executive functioning and/or externalizing behaviors. In some studies, gains related to internalizing symptoms were found too. The meta-analytic model conducted on the combined mean of all behavioral outcomes of studies (model Behavioral A) yielded an estimate effect of small-to-moderate level ($g = 0.37$), which points to positive effects of behavioral TP. This effect was confirmed also by the meta-analytic model considering the outcome associated with the highest improvement ($g = 0.40$; model Behavioral B). A possible explanation for this finding is that the different questionnaires assessing behavioral competences comprised some items evaluating similar behaviors, irrespective of the fact that they were aimed at assessing everyday cognitive functioning, psychological adjustment, or social behaviors. Thus, the selection of the behavioral domain generating the highest effect did not have an impact on results, in contrast to what was observed for cognitive TP.

As aggressive behavior, mood lability, and social isolation have been frequently reported for patients with ABI and appear to increase with age [11, 78], the remote behavioral TP reviewed in the present work may constitute valid alternatives to rehabilitation treatments on these aspects. The success of behavioral TP could be in part attributed to the direct and strong involvement of family members, which recurred in 6 out of the 7 studies included in the meta-analytic exploration. Indeed, family involvement seems to promote generalization of the effects of rehabilitation interventions on children [55, 79, 80]. Nevertheless, one study focused on a behavioral training providing support of peers instead of involvement of family members [57]. Thus, a continuative and structured involvement of other agents, not specifically confined to relatives, may be associated with successful effects of behavioral telerehabilitation.

Nevertheless, also for behavioral studies, a high level of methodological heterogeneity emerged from statistical analyses, despite TP methodology and sample diagnosis were similar across the various studies. Thus, total heterogeneity could likely be due to differences in specific demographic or clinical characteristics of enrolled children or families. This explanation seems to be in line with indications provided by the members of the research team studying behavioral TP [24–26], suggesting that it could be worth for future research to weigh the impact of those specific variables related to the children or the families that may moderate training efficacy. Such an investigation could allow identifying the specific characteristics of individuals that are more likely to benefit from behavioral TP.

It is worth noting that the efficacy of behavioral TP was assessed through questionnaires, which may be affected by expectation bias associated with the fact that patients/parents know they/their children are receiving a treatment and thus may overestimate changes after the intervention (e.g., [81, 82]). This expectation bias can be controlled with a successful blinding. However, given the nature of the included studies on behavioral TP, participants could not be blinded from group assignment (see [15]). In this regard, the introduction of performance-based measures may represent a suitable option to consider for future research with the aim to assess the behavioral effects of these TP and, at the same time, to ensure better methodological procedures and enhance validity. Nowadays, performance-based assessment to investigate everyday executive function behaviors [83, 84] or sociocognitive functioning through virtual reality tools [85, 86] has been described in the relevant literature, thus representing a feasible method to adopt.

4.1. Limitations of This Review. In this work, we included research on TP only published in English, which could have led to the omission of relevant research on this issue. Moreover, even though our search strategy was thought to minimize the risk to omit relevant research, as it was based on (i) adoption of two widely used comprehensive databases, namely PubMed and Scopus, (ii) identification of studies reported in recently published meta-analyses and reviews on the topic, and lastly, (iii) search of relevant research on the websites of the main TP, it is still possible that some pertinent records may have been missed out. Second, study heterogeneity was high for both cognitive and behavioral TP, which could have affected results and limited the generalizability of conclusions. The relatively small number of studies inserted in the meta-analytic examinations prevented the possibility to conduct more detailed subgroup analyses aimed at exploring the contribution of specific variables on outcomes, leaving to future research the interesting task of clarifying which components of remote TP lead to the best effects. On a related note, data of this meta-analysis are limited to those studies having a control group, thus representing only a half of the studies on TP addressing cognitive

functions. Finally, the evaluation of training efficacy in this work was confined to post-training outcomes, thus preventing any conclusions on long-term effects.

5. Conclusions

In summary, results of the present work suggest that remote computer-based TP with a cognitive or a behavioral focus for pediatric ABI may be effective in improving children's functioning. This was confirmed both by the review process and by the meta-analytic investigation. The possibility to address cognitive and behavioral impairments by delivering home-based treatments should be considered as a relevant opportunity for the rehabilitation course of these children. Indeed, TP delivered in ecological settings may help overcome the limited availability of services outside the clinical centers or the urban areas and limit the time and economic demands to families associated with reaching the hospitals [12, 29]. Nevertheless, the high methodological heterogeneity of studies prevents us from drawing definite conclusions. Future research is required to verify the effects of remote TP addressing cognitive and behavioral functions in specific populations of children with ABI based on precise etiology, age range, intellectual competence, and family socioeconomic status. However, despite methodological limitations, a consistent finding of this study is the improvement of visuo-spatial abilities after a computerized intervention addressing cognitive functions. This result is in accordance with data reported in the literature on healthy individuals [75–77] and suggests that the usefulness of drill-based computerized cognitive interventions to enhance visuo-spatial abilities also occurs in case of damage to a developing central nervous system.

Conflicts of Interest

Authors declare that no conflict of interest exists.

Authors' Contributions

Claudia Corti and Viola Oldrati contributed equally to this work.

Acknowledgments

We thank Drs. Paul Bangirana, Amery Treble-Barna, Suncica Lah, and Natalie Phillips who generously provided elucidations on their research upon our request. We also want to thank Dr. Monica Martignoni for the help provided in revising the final version of the manuscript as part of her internship activities. This study was supported by the Italian Ministry of Health (Ricerca Finalizzata NET-2013-02356160-4 to Renato Borgatti; Ricerca Corrente 2018/2019 to Renato Borgatti) and by the "5 per mille" funds 2018/2019 for biomedical research to Alessandra Bardoni.

References

[1] B. Slomine and G. Locascio, "Cognitive rehabilitation for children with acquired brain injury," *Developmental Disabilities Research Reviews*, vol. 15, no. 2, pp. 133–143, 2009.

[2] S. Gazzellini, S. Strazzer, M. Stortini et al., "Pediatric rehabilitation of severe acquired brain injury: a multicenter survey," *European Journal of Physical and Rehabilitation Medicine*, vol. 48, no. 3, pp. 423–431, 2012.

[3] M. C. Dewan, N. Mummareddy, J. C. Wellons III, and C. M. Bonfield, "Epidemiology of global pediatric traumatic brain injury: qualitative review," *World neurosurgery*, vol. 91, pp. 497–509.e1, 2016.

[4] D. J. Thurman, "The epidemiology of traumatic brain injury in children and youths: a review of research since 1990," *Journal of Child Neurology*, vol. 31, no. 1, pp. 20–27, 2016.

[5] C. Corti, V. Manfredi, M. Massimino, A. Bardoni, R. Borgatti, and G. Poggi, "Cognitive functioning of pediatric patients with brain tumor: an investigation of the role of gender," *Child's Nervous System*, vol. 34, no. 12, pp. 2415–2423, 2018.

[6] C. Corti, G. Poggi, M. Massimino, A. Bardoni, R. Borgatti, and C. Urgesi, "Visual perception and spatial transformation of the body in children and adolescents with brain tumor," *Neuropsychologia*, vol. 120, pp. 124–136, 2018.

[7] M. N. Gragert and M. D. Ris, "Neuropsychological late effects and rehabilitation following pediatric brain tumor," *Journal of Pediatric Rehabilitation Medicine*, vol. 4, no. 1, pp. 47–58, 2011.

[8] V. Anderson, C. Godfrey, J. V. Rosenfeld, and C. Catroppa, "10 years outcome from childhood traumatic brain injury," *International Journal of Developmental Neuroscience*, vol. 30, no. 3, pp. 217–224, 2012.

[9] C. Catroppa, C. Godfrey, J. V. Rosenfeld, S. S. J. C. Hearps, and V. A. Anderson, "Functional recovery ten years after pediatric traumatic brain injury: outcomes and predictors," *Journal of Neurotrauma*, vol. 29, no. 16, pp. 2539–2547, 2012.

[10] V. Anderson, M. H. Beauchamp, K. O. Yeates et al., "Social competence at two years after childhood traumatic brain injury," *Journal of Neurotrauma*, vol. 34, no. 14, pp. 2261–2271, 2017.

[11] P. Geraldina, L. Mariarosaria, A. Annarita et al., "Neuropsychiatric sequelae in TBI: a comparison across different age groups," *Brain Injury*, vol. 17, no. 10, pp. 835–846, 2003.

[12] S. L. Wade, M. E. Narad, E. L. Shultz et al., "Technology-assisted rehabilitation interventions following pediatric brain injury," *Journal of Neurosurgical Sciences*, vol. 62, no. 2, pp. 187–202, 2018.

[13] M. Ylvisaker, L. S. Turkstra, and C. Coelho, "Behavioral and social interventions for individuals with traumatic brain injury: a summary of the research with clinical implications," *Seminars in Speech and Language*, vol. 26, no. 04, pp. 256–267, 2005.

[14] M. A. Linden, A. E. Glang, and A. Mckinlay, "A systematic review and meta-analysis of educational interventions for children and adolescents with acquired brain injury," *NeuroRehabilitation*, vol. 42, no. 3, pp. 311–323, 2018.

[15] M. Linden, C. Hawley, B. Blackwood, J. Evans, V. Anderson, and C. O'Rourke, "Technological aids for the rehabilitation of memory and executive functioning in children and adolescents with acquired brain injury," *The Cochrane Database of Systematic Reviews*, vol. 7, article CD011020, 2016.

[16] S. Lindsay, L. R. Hartman, N. Reed, C. Gan, N. Thomson, and B. Solomon, "A systematic review of hospital-to-school reintegration interventions for children and youth with acquired brain injury," *PLoS One*, vol. 10, no. 4, article e0124679, 2015.

[17] C. Resch, S. Rosema, P. Hurks, A. de Kloet, and C. van Heugten, "Searching for effective components of cognitive rehabilitation for children and adolescents with acquired brain injury: a systematic review," *Brain Injury*, vol. 32, no. 6, pp. 679–692, 2018.

[18] M. Semrud-Clikeman, "Pediatric traumatic brain injury: rehabilitation and transition to home and school," *Applied Neuropsychology*, vol. 17, no. 2, pp. 116–122, 2010.

[19] D. R. Shaw, "Pediatric cognitive rehabilitation: effective treatments in a school-based environment," *NeuroRehabilitation*, vol. 34, no. 1, pp. 23–28, 2014.

[20] D. R. Shaw, "A systematic review of pediatric cognitive rehabilitation in the elementary and middle school systems," *NeuroRehabilitation*, vol. 39, no. 1, pp. 119–123, 2016.

[21] S. R. Kesler, N. J. Lacayo, and B. Jo, "A pilot study of an online cognitive rehabilitation program for executive function skills in children with cancer-related brain injury," *Brain Injury*, vol. 25, no. 1, pp. 101–112, 2011.

[22] S. L. Wade, N. C. Walz, J. C. Carey, and K. M. Williams, "Preliminary efficacy of a Web-based family problem-solving treatment program for adolescents with traumatic brain injury," *The Journal of Head Trauma Rehabilitation*, vol. 23, no. 6, pp. 369–377, 2008.

[23] S. L. Wade, N. C. Walz, J. Carey et al., "A randomized trial of teen online problem solving for improving executive function deficits following pediatric traumatic brain injury," *The Journal of Head Trauma Rehabilitation*, vol. 25, no. 6, pp. 409–415, 2010.

[24] S. P. Raj, N. Zhang, M. W. Kirkwood et al., "Online family problem solving for pediatric traumatic brain injury: influences of parental marital status and participation on adolescent outcomes," *Journal of Head Trauma Rehabilitation*, vol. 33, no. 3, pp. 158–166, 2018.

[25] S. L. Wade, E. E. Kaizar, M. Narad et al., "Online family problem-solving treatment for pediatric traumatic brain injury," *Pediatrics*, vol. 142, no. 6, article e20180422, 2018.

[26] N. Zhang, E. E. Kaizar, M. E. Narad et al., "Examination of injury, host, and social-environmental moderators of online family problem solving treatment efficacy for pediatric traumatic brain injury using an individual participant data meta-analytic approach," *Journal of Neurotrauma*, vol. 36, no. 7, pp. 1147–1155, 2019.

[27] T.-V. How, A. S. Hwang, R. E. A. Green, and A. Mihailidis, "Envisioning future cognitive telerehabilitation technologies: a co-design process with clinicians," *Disability and Rehabilitation: Assistive Technology*, vol. 12, no. 3, pp. 244–261, 2017.

[28] M. Zampolini, E. Todeschini, M. Bernabeu Guitart et al., "Tele-rehabilitation: present and future," *Annali dell'Istituto superiore di sanita*, vol. 44, no. 2, pp. 125–134, 2008.

[29] C. Corti, G. Poggi, R. Romaniello et al., "Feasibility of a home-based computerized cognitive training for pediatric patients with congenital or acquired brain damage: an explorative study," *PLoS One*, vol. 13, no. 6, article e0199001, 2018.

[30] J. Concato, N. Shah, and R. I. Horwitz, "Randomized, controlled trials, observational studies, and the hierarchy of research designs," *New England Journal of Medicine*, vol. 342, no. 25, pp. 1887–1892, 2000.

[31] M. Ferriter and N. Huband, "Does the non-randomized controlled study have a place in the systematic review? A pilot study," *Criminal Behaviour and Mental Health*, vol. 15, no. 2, pp. 111–120, 2005.

[32] S. J. Suskauer, K. O. Yeates, K. Sarmiento et al., "Strengthening the evidence base: recommendations for future research identified through the development of CDC's pediatric mild TBI guideline," *Journal of Head Trauma Rehabilitation*, vol. 34, no. 4, pp. 215–223, 2019.

[33] A. Treble-Barna, M. M. Sohlberg, B. E. Harn, and S. L. Wade, "Cognitive intervention for attention and executive function impairments in children with traumatic brain injury: a pilot study," *The Journal of Head Trauma Rehabilitation*, vol. 31, no. 6, pp. 407–418, 2016.

[34] A. J. de Kloet, M. A. M. Berger, I. M. A. J. Verhoeven, K. van Stein Callenfels, and T. P. M. V. Vlieland, "Gaming supports youth with acquired brain injury? A pilot study," *Brain Injury*, vol. 26, no. 7-8, pp. 1021–1029, 2012.

[35] P. Bangirana, P. Allebeck, M. J. Boivin et al., "Cognition, behaviour and academic skills after cognitive rehabilitation in Ugandan children surviving severe malaria: a randomised trial," *BMC Neurology*, vol. 11, no. 1, p. 96, 2011.

[36] P. Bangirana, B. Giordani, C. C. John, C. Page, R. O. Opoka, and M. J. Boivin, "Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors," *Journal of Developmental & Behavioral Pediatrics*, vol. 30, no. 4, pp. 310–318, 2009.

[37] R. W. Butler, D. R. Copeland, D. L. Fairclough et al., "A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy," *Journal of Consulting and Clinical Psychology*, vol. 76, no. 3, pp. 367–378, 2008.

[38] A. A. King, D. A. White, R. C. McKinstry, M. Noetzel, and M. R. DeBaun, "A pilot randomized education rehabilitation trial is feasible in sickle cell and strokes," *Neurology*, vol. 68, no. 23, pp. 2008–2011, 2007.

[39] C. Catroppa, K. Stone, S. J. C. Hearps, C. Soo, V. Anderson, and S. Rosema, "Evaluation of an attention and memory intervention post-childhood acquired brain injury: preliminary efficacy, immediate and 6 months post-intervention," *Brain Injury*, vol. 29, no. 11, pp. 1317–1324, 2015.

[40] N. M. Sjö, S. Spellerberg, S. Weidner, and M. Kihlgren, "Training of attention and memory deficits in children with acquired brain injury," *Acta Paediatrica*, vol. 99, no. 2, pp. 230–236, 2010.

[41] I. van't Hooft, K. Andersson, B. Bergman, T. Sejersen, L. von Wendt, and A. Bartfai, "Beneficial effect from a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study," *Brain Injury*, vol. 19, no. 7, pp. 511–518, 2005.

[42] I. van't Hooft, K. Andersson, B. Bergman, T. Sejersen, L. Von Wendt, and A. Bartfai, "Sustained favorable effects of cognitive training in children with acquired brain injuries," *NeuroRehabilitation*, vol. 22, no. 2, pp. 109–116, 2007.

[43] E. Dvorak and C. van Heugten, "A summary on the effectiveness of the Amsterdam memory and attention training for children (Amat-c) in children with brain injury," *Brain Injury*, vol. 32, no. 1, pp. 18–28, 2018.

[44] B. Carlson-Green, J. Puig, and A. Bendel, "Feasibility and efficacy of an extended trial of homebased working memory training for pediatric brain tumor survivors: a pilot study," *Neuro-Oncology Practice*, vol. 4, no. 2, article npw015, 2017.

[45] H. M. Conklin, J. M. Ashford, K. N. Clark et al., "Long-term efficacy of computerized cognitive training among survivors of childhood cancer: a single-blind randomized controlled

trial," *Journal of Pediatric Psychology*, vol. 42, no. 2, pp. 220–231, 2017.

[46] H. M. Conklin, R. J. Ogg, J. M. Ashford et al., "Computerized cognitive training for amelioration of cognitive late effects among childhood cancer survivors: a randomized controlled trial," *Journal of Clinical Oncology*, vol. 33, no. 33, pp. 3894–3902, 2015.

[47] K. K. Hardy, V. W. Willard, T. M. Allen, and M. J. Bonner, "Working memory training in survivors of pediatric cancer: a randomized pilot study," *Psychooncology*, vol. 22, no. 8, pp. 1856–1865, 2013.

[48] S. L. Wade, G. Bedell, J. A. King et al., "Social Participation and Navigation (SPAN) program for adolescents with acquired brain injury: pilot findings," *Rehabilitation Psychology*, vol. 63, no. 3, pp. 327–337, 2018.

[49] N. Scammacca, G. Roberts, and K. K. Stuebing, "Meta-analysis with complex research designs: dealing with dependence from multiple measures and multiple group comparisons," *Review of Educational Research*, vol. 84, no. 3, pp. 328–364, 2014.

[50] N. L. Phillips, A. Mandalis, S. Benson et al., "Computerized working memory training for children with moderate to severe traumatic brain injury: a double-blind, randomized, placebo-controlled trial," *Journal of Neurotrauma*, vol. 33, no. 23, pp. 2097–2104, 2016.

[51] A. Piovesana, S. Ross, O. Lloyd et al., "A randomised controlled trial of a web-based multi-modal therapy program to improve executive functioning in children and adolescents with acquired brain injury," *Clinical Rehabilitation*, vol. 31, no. 10, pp. 1351–1363, 2017.

[52] L. Sakzewski, M. J. Lewis, L. McKinlay, J. Ziviani, and R. N. Boyd, "Impact of multi-modal web-based rehabilitation on occupational performance and upper limb outcomes: pilot randomized trial in children with acquired brain injuries," *Developmental Medicine & Child Neurology*, vol. 58, no. 12, pp. 1257–1264, 2016.

[53] B. G. Kurowski, S. L. Wade, M. W. Kirkwood, T. M. Brown, T. Stancin, and H. G. Taylor, "Online problem-solving therapy for executive dysfunction after child traumatic brain injury," *Pediatrics*, vol. 132, no. 1, pp. e158–e166, 2013.

[54] S. J. Tlustos, M. W. Kirkwood, H. G. Taylor, T. Stancin, T. M. Brown, and S. L. Wade, "A randomized problem-solving trial for adolescent brain injury: changes in social competence," *Rehabilitation Psychology*, vol. 61, no. 4, pp. 347–357, 2016.

[55] S. L. Wade, J. Carey, and C. R. Wolfe, "The efficacy of an online cognitive-behavioral family intervention in improving child behavior and social competence following pediatric brain injury," *Rehabilitation Psychology*, vol. 51, no. 3, pp. 179–189, 2006.

[56] S. L. Wade, T. Stancin, M. Kirkwood, T. M. Brown, K. M. McMullen, and H. G. Taylor, "Counselor-assisted problem solving (CAPS) improves behavioral outcomes in older adolescents with complicated mild to severe TBI," *The Journal of Head Trauma Rehabilitation*, vol. 29, no. 3, pp. 198–207, 2014.

[57] S. L. Wade, H. G. Taylor, K. O. Yeates et al., "Online problem solving for adolescent brain injury: a randomized trial of 2 approaches," *Journal of Developmental and Behavioral Pediatrics*, vol. 39, no. 2, pp. 154–162, 2018.

[58] S. L. Wade, N. C. Walz, J. Carey et al., "Effect on behavior problems of teen online problem-solving for adolescent traumatic brain injury," *Pediatrics*, vol. 128, no. 4, pp. e947–e953, 2011.

[59] L. V. Hedges and I. Olkin, *Statistical Methods for Meta-Analysis*, Academic Press, Cambridge (Massachuseets), 1985.

[60] J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring inconsistency in meta-analyses," *BMJ*, vol. 327, no. 7414, pp. 557–560, 2003.

[61] C. B. Begg and M. Mazumdar, "Operating characteristics of a rank correlation test for publication bias.," *Biometrics*, vol. 50, no. 4, pp. 1088–1101, 1994.

[62] T. R. Levine, K. J. Asada, and C. Carpenter, "Sample sizes and effect sizes are negatively correlated in meta-analyses: evidence and implications of a publication bias against nonsignificant findings," *Communication Monographs*, vol. 76, no. 3, pp. 286–302, 2009.

[63] W. Viechtbauer, "Conducting meta-analyses in R with the metafor package," *Journal of Statistical Software*, vol. 36, pp. 1–48, 2010.

[64] M. Eve, F. O'Keeffe, S. Jhuty, V. Ganesan, G. Brown, and T. Murphy, "Computerized working-memory training for children following arterial ischemic stroke: a pilot study with long-term follow-up," *Applied Neuropsychology-Child*, vol. 5, no. 4, pp. 273–282, 2016.

[65] K. K. Hardy, V. W. Willard, and M. J. Bonner, "Computerized cognitive training in survivors of childhood cancer a pilot study," *Journal of Pediatric Oncology Nursing*, vol. 28, no. 1, pp. 27–33, 2011.

[66] M. M. Sohlberg, B. Harn, H. MacPherson, and S. L. Wade, "A pilot study evaluating attention and strategy training following pediatric traumatic brain injury," *Clinical Practice in Pediatric Psychology*, vol. 2, no. 3, pp. 263–280, 2014.

[67] C. Vander Linden, H. Verhelst, E. Deschepper, G. Vingerhoets, K. Deblaere, and K. Caeyenberghs, "Cognitive training benefit depends on brain injury location in adolescent with traumatic brain injury: a pilot study," *European Journal of Physical and Rehabilitation Medicine*, 2018.

[68] H. Verhelst, C. Vander Linden, G. Vingerhoets, and K. Caeyenberghs, "How to train an injured brain? A pilot feasibility study of home-based computerized cognitive training," *Games for Health Journal*, vol. 6, no. 1, pp. 28–38, 2017.

[69] B. G. Kurowski, S. L. Wade, M. W. Kirkwood, T. M. Brown, T. Stancin, and H. G. Taylor, "Long-term benefits of an early online problem-solving intervention for executive dysfunction after traumatic brain injury in children," *JAMA Pediatrics*, vol. 168, no. 6, pp. 523–531, 2014.

[70] S. L. Wade, B. G. Kurowski, M. W. Kirkwood et al., "Online problem-solving therapy after traumatic brain injury: a randomized controlled trial," *Pediatrics*, vol. 135, no. 2, pp. e487–e495, 2015.

[71] S. L. Wade, H. G. Taylor, A. Cassedy et al., "Long-term behavioral outcomes after a randomized, clinical trial of counselor-assisted problem solving for adolescents with complicated mild-to-severe traumatic brain injury," *Journal of Neurotrauma*, vol. 32, no. 13, pp. 967–975, 2015.

[72] S. L. Wade, C. Wolfe, T. M. Brown, and J. P. Pestian, "Putting the pieces together: preliminary efficacy of a web-based family intervention for children with traumatic brain injury," *Journal of Pediatric Psychology*, vol. 30, no. 5, pp. 437–442, 2005.

[73] M. E. Narad, G. Bedell, J. A. King et al., "Social Participation and Navigation (SPAN): description and usability of app-based coaching intervention for adolescents with TBI," *Developmental Neurorehabilitation*, vol. 21, no. 7, pp. 439–448, 2018.

[74] J. Cohen, *Statistical Analysis and Power for the Behavioral Sciences*, Erinbaum, Hillsdale, NJ, USA, 2nd edition edition, 1988.

[75] C. S. Green and D. Bavelier, "Action-video-game experience alters the spatial resolution of vision," *Psychological Science*, vol. 18, no. 1, pp. 88–94, 2007.

[76] R. J. Haier, S. Karama, L. Leyba, and R. E. Jung, "MRI assessment of cortical thickness and functional activity changes in adolescent girls following three months of practice on a visual-spatial task," *BMC Research Notes*, vol. 2, no. 1, p. 174, 2009.

[77] A. Lau-Zhu, E. A. Holmes, S. Butterfield, and J. Holmes, "Selective association between Tetris game play and visuospatial working memory: a preliminary investigation," *Applied Cognitive Psychology*, vol. 31, no. 4, pp. 438–445, 2017.

[78] M. Ylvisaker, L. Turkstra, C. Coehlo et al., "Behavioural interventions for children and adults with behaviour disorders after TBI: a systematic review of the evidence," *Brain Injury*, vol. 21, no. 8, pp. 769–805, 2007.

[79] K. E. Holm, J. M. Patterson, and J. G. Gurney, "Parental involvement and family-centered care in the diagnostic and treatment phases of childhood cancer: results from a qualitative study," *Journal of Pediatric Oncology Nursing*, vol. 20, no. 6, pp. 301–313, 2003.

[80] H. G. Taylor, K. O. Yeates, S. L. Wade, D. Drotar, T. Stancin, and N. Minich, "A prospective study of short- and long-term outcomes after traumatic brain injury in children: behavior and achievement," *Neuropsychology*, vol. 16, no. 1, pp. 15–27, 2002.

[81] J. Alcantara, J. Ohm, and J. Alcantara, "Comparison of pediatric self reports and parent proxy reports utilizing PROMIS?: results from a chiropractic practice-based research network," *Complementary Therapies in Clinical Practice*, vol. 29, pp. 48–52, 2017.

[82] L. M. Nielsen, H. Kirkegaard, L. G. Østergaard, K. Bovbjerg, K. Breinholt, and T. Maribo, "Comparison of self-reported and performance-based measures of functional ability in elderly patients in an emergency department?: implications for selection of clinical outcome measures," *BMC Geriatrics*, vol. 16, no. 1, p. 199, 2016.

[83] M. P. Chevignard, C. Taillefer, C. Picq, F. Poncet, M. Noulhiane, and P. Pradat-Diehl, "Ecological assessment of the dysexecutive syndrome using execution of a cooking task," *Neuropsychological Rehabilitation*, vol. 18, no. 4, pp. 461–485, 2008.

[84] K. Rocke, P. Hays, D. Edwards, and C. Berg, "Development of a performance assessment of executive function: the Children's Kitchen Task Assessment," *American Journal of Occupational Therapy*, vol. 62, no. 5, pp. 528–537, 2008.

[85] S. Bioulac, E. de Sevin, P. Sagaspe et al., "What do virtual reality tools bring to child and adolescent psychiatry?," *L'Encéphale*, vol. 44, no. 3, pp. 280–285, 2018.

[86] Y. Gilboa, H. Fogel-Grinvald, and M. Chevignard, "Virtual classroom assessment for children and adolescents with attention deficits: a systematic review and meta-analysis of measurement properties," *Journal of Attention Disorders*, 2018.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 9268179, 7 pages
https://doi.org/10.1155/2019/9268179

Research Article

Improving Cognitive Function after Traumatic Brain Injury: A Clinical Trial on the Potential Use of the Semi-Immersive Virtual Reality

Rosaria De Luca, Maria Grazia Maggio, Giuseppa Maresca, Desiree Latella, Antonino Cannavò, Francesca Sciarrone, Emanuele Lo Voi, Maria Accorinti, Placido Bramanti, and Rocco Salvatore Calabrò

IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy

Correspondence should be addressed to Rocco Salvatore Calabrò; salbro77@tiscali.it

Received 29 January 2019; Accepted 15 July 2019; Published 30 July 2019

Guest Editor: Mary H. Kosmidis

Copyright © 2019 Rosaria De Luca et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Traumatic brain injury (TBI) is the most common cause of long-term disability and death among young adults, and it represents an enormous socioeconomic and healthcare burden. Our purpose is to evaluate the effects of a virtual reality training with BTs-Nirvana (BTs-N) on the recovery of cognitive functions in TBI subjects, using the interactive semi-immersive program. One hundred patients with TBI were enrolled in this study and randomized into either the Traditional Cognitive Rehabilitation Group (TCRG: $n = 50$) or the Virtual Reality Training Group (VRTG: $n = 50$). The VRTG underwent a VRT with BTs-N, whereas the TCRG received a standard cognitive treatment. Each treatment session lasted 60 minutes and was repeated three times a week for 8 weeks. All of the patients were evaluated by a specific psychometric battery before (T0) and immediately (T1) after the end of the training. VRTG and TCRG had a significant improvement in cognitive functioning and in mood, but only VRTG presented with a significant increase in cognitive flexibility and shifting skills and in selective attention. In conclusion, our results suggest that VR may be a useful and effective approach for the rehabilitation of patients with TBI, leading to better cognitive and behavioral outcomes.

1. Introduction

Traumatic brain injury (TBI) is a condition caused by a mechanical event that causes skull and/or brain damage due to a strong and violent head blow (i.e., falls and sport injuries), strong rotations of the head (i.e., road accidents), or penetration of objects in the cranium (i.e., bullets) thus causing focal or diffuse damage to multiple brain areas [1]. TBI is the most common cause of long-term disability and death among young adults, and it represents an enormous socioeconomic and healthcare burden [2]. It is estimated that about 5.48 million people suffer from severe TBI each year (73 cases per 100,000 people) [3]. Among the survivors of moderate to severe head injury, 31.8% of patients die or need hospitalization in a specialized health center; 44% are unable to return to work, and 88% of the patients with mild TBI have white matter damage, with negative repercussions on functional outcomes [4]. In fact, TBI may affect motor, cognitive, emotional, and psychological functions with a consequent worsening of both patient and his/her caregiver's quality of life [5]. In particular, cognitive dysfunction may interfere with work, relationships, leisure, and daily activities, increasing the burden of the disease [6, 7]. Growing evidence demonstrates that cognitive rehabilitation (CR), through previously learned skills or new compensatory strategies, is effective in patients with TBI as it enhances cognitive and psychosocial interaction [8–12]. In recent years, technological innovations have allowed the development of new rehabilitative strategies, such as PC-based rehabilitation or Virtual Reality Training (VRT), which have proven effective in the CR of neurological patients [13–16]. Chen et al. [17], examining the efficacy of PC-based rehabilitation in TBI

Table 1: Demographic characteristics at baseline for both of the groups.

	Virtual Reality Training Group	Traditional Cognitive Rehabilitation Group	All	p value
Participants	50	50	100	
Age	38.7 ± 9.3	41.1 ± 10.8	39.9 ± 10.1	0.22
Education	2.9 ± 0.8	2.7 ± 0.8	2.8 ± 0.850	0.23
Gender				0.69
Male	29 (57.9%)	26 (52%)	56 (56%)	
Female	21 (42.1%)	24 (48%)	44 (44%)	
Interval from TBI				
Mean in months	4.5 ± 1.5	4 ± 2	4.7 ± 1.3	0.78
Brain lesion site/side				
Cortical right	22	24	46	
Subcortical right	16	17	33	
Cortical left	8	6	14	
Subcortical left	4	3	7	

Quantitative variables were expressed as means ± standard deviations, categorical variables as frequencies and percentages.

subjects, observed significant posttreatment improvements on cognitive domains. Moreover, it has been demonstrated that PC cognitive training can be a potential CR strategy to optimize cognitive and global functional recovery [18, 19]. Several studies using VR have shown that it increases cognitive and behavioral skills in patients with TBI [13–16]. Indeed, it has been demonstrated that VR may be effective in improving executive functions in patients with TBI in the subacute phase [20]. In a recent review, Maggio et al. [9] found that VR might positively affect memory, attention, executive function, behavior, and mood in individuals with TBI. Indeed, evidence of the use of VR in TBI cognitive neurorehabilitation is very poor and there is not enough consensus on its use in the context of TBI rehabilitation [13].

The aim of this study is to evaluate the effects of a VRT using BTs-Nirvana (BTs-N) for the recovery of cognitive and behavioral functions in patients with TBI through an interactive semi-immersive program.

Figure 1: A patient affected by traumatic brain injury performing cognitive training in the semi-immersive virtual scenario created by BTs-Nirvana.

2. Material and Methods

2.1. Study Population. One hundred patients with TBI (mean ± SD age: 39.93 ± 10.1 years; 56% males), who attended our Behavioral and Robotic Neurorehabilitation Service from January 2016 to December 2018, were enrolled in this study and randomized in order to be recruited into either the Traditional CR Group (TCRG: $n = 50$) or the VRT Group (VRTG: $n = 50$) (Table 1). Inclusion criteria were (i) neurological diagnosis of mild to moderate TBI in the postacute phase (i.e., 3 to 6 months from the acute event), (ii) ability to sit for at least 20 minutes (including at least one minute without support), and (iii) presence of mild to moderate cognitive impairment (Montreal Cognitive Assessment (MoCA) from 18 to 25 [21]). Exclusion criteria were (i) age > 85 years, (ii) presence of disabling sensory alterations and frequent episodes of recurrent epilepsy (especially positive symptoms such as audio-video hallucination), and (iii) concomitant medical and psychiatric illness possibly interfering with the VR training.

2.2. Study Design. All of the patients underwent the same amount of CR, but using different tools. TCRG underwent traditional CR, administered in individual sessions using a face-to-face interaction between therapist and patient with paper and pencil activities, whereas VRTG performed a VRT using BTs-N. VR allows a multisensory and interactive simulation of scenarios that affect real life with the aid of a computer. The recreated situations are generally three-dimensional and reproduce real objects and events, improving the cognitive abilities of patients. In particular, BTs-N is a semi-immersive therapy program, for motor and cognitive rehabilitation, which offers interactive virtual scenarios in which patient carries out the training with the help of a

Table 2: TBI cognitive rehabilitative program.

Cognitive domain	Conventional cognitive rehabilitation	Cognitive training by BTs-Nirvana
Executive functions	The patient uses tools, such as a pencil, sheets, and a pen, to perform exercises in a specific physical space (rehabilitation table); the exercises can also provide tasks of simple associations (i.e., letter-color), inhibitory control, and arithmetic operations; estimating the numerical quantity and the categorization; and the deductive logical reasoning.	The patient performs exercises in a virtual environment through the movement performed in the interactive screen. The movements allow to move or manipulate specific objects, in different directions (i.e., balls, flowers, and butterfly), or to create specific associations (i.e., color-number) with a dynamic interaction in the virtual environment. When the patient touches the virtual objects, he/she determines an audio and video feedback (using the sprite activity). In particular, the subject can perform ideomotor sequences with the guidance of the therapist, calculation and numerical processing, inhibitory control, and arithmetic operations; can estimate the numerical quantity and the categorization; and can perform the deductive logical reasoning, using a specific virtual task.
	Rehabilitative resources: face-to-face rehabilitative session between the patient and the therapist, using paper and pencil materials.	*Virtual scenarios*: The Bricklaying Tools; Hopscotch; The Colour of Fruit; Walk Through; and Eggs Circle.
	Each training is divided into three different levels of difficulty in relation to the complexity of the tasks, the number of errors, or the speed of execution of the exercise.	The difficulty level increases (from the first to the third level) with the increment of the complexity of the virtual task, elements on the screen, and greater difficulty of the requests by the therapist.
Attention processes and visual-spatial cognition	The patient must indicate and touch specific target stimuli in relation to specific characteristics (color, image, animal, function, etc.), neglecting the distractors. The therapist gives verbal deliveries to the patient, combining the image corresponding to the selection (which reflects the characteristics of the objects to choose).	The patient selects/explores some elements (colors, musical arcs, geometric shapes or not, animals, etc.) observed in the virtual environment. These elements remain visible to the observer for a variable time, established by the interaction between the virtual system, the therapist, and the patient. The patient touches the virtual target element, at a specific time; this action causes a visual change with a typical audio/video feedback (positive reinforcement); otherwise, the element disappears (negative reinforcement) (Hunt task).
	Rehabilitative resources: face-to-face rehabilitative session between patient and therapist, use of paper and pencil materials.	*Virtual scenarios*: Billiards, Piano, Storm, Flowerized, and Goal.
	Cognitive therapist structures tasks with increased difficulty, according to specific parameters such as number and type target, number and type of distractor, and complexity of consign.	*The level of difficulty increases with the increase of the numbers of distractors and reducing the usable time of execution.*

therapist. The patient interacts with virtual scenarios and audio-visual stimuli through movement, creating a total sensory involvement that facilitates rehabilitation of attention, visual-spatial, and executive skills (Figure 1). All patients (TCRG and VRTG) underwent a total of 24 1 h sessions (3 times a week for 8 weeks). Both groups underwent the same conventional physiotherapy program, aimed at improving muscle strength, coordination, and spasticity. The detailed rehabilitative program in both groups is described in detail in Table 2.

2.3. Outcome Measures. Each participant was assessed by means of a neuropsychological evaluation before (T0) and immediately after the end of the training (T1). A skilled neuropsychologist administered a battery of tests including Montreal Cognitive Assessment (MoCA) [21] to assess the general cognitive state; Hamilton Rating Scale Depression (HRS-D) [22] and Hamilton Rating Scale Anxiety (HRS-A) [23] to assess mood and anxiety, respectively; Frontal Assessment Battery (FAB) [24] and Weigl's Test [25] to evaluate frontal abilities; and Visual Search (VS) [26] and Trial Making Test (TMT) [27] to measure the attention process, attentive shifting, and visual research abilities.

The present study was conducted in accordance with the 1964 Helsinki Declaration and approved by our Research Institute Ethics Committee (ID 25/2015); written informed consent was obtained from all participants.

2.4. Data Analysis. Data were analyzed using the SPSS 16.0 version, considering a $p < 0.05$ as statistically significant. Using SPSS, we performed the analysis of variance (ANOVA) in order to assess whether the type of treatment influenced the clinical outcome, independently from the score difference at baseline. The dependent variable consisted in the performances obtained in tests of the different cognitive functions; the categorical variable was the "Group" (1 = VRTG; 2 = TCRG); instead, the variable was "Time" (factor within the subject with two levels: T0 and T1). Finally, the independent variable consisted of scales/tests to evaluate neuropsychological functions and mood. Student's t-tests, using the Bonferroni correction, were used for post hoc testing of group differences in time and performance.

3. Results

All of the patients completed the training program without any adverse events, including cyber-sickness. No significant differences were found in age ($p = 0.22$), sex ($p = 0.22$), and education ($p = 0.69$) between VRTG and TCRG. At baseline, no significant differences emerged between the test scores of the two groups. The ANOVA showed the triple interaction between Group*Time*Tests/Scales ($F_{(9162)} = 21741$, $p < 0.001$). In particular, ANOVA decomposition (Table 3) highlighted how the effect of the two treatments was significantly different, influencing the scores of all tests/scales. Post hoc analysis results (Table 4) showed that VRTG and TCRG had a significant improvement in various cognitive functioning and mood. However, we observed a significant increase in cognitive flexibility and shifting skills (TMT B-A) and in selective attention/visual research (VS) only in the VRTG. Moreover, at T1, we found a significant difference between VRTG and TCRG for all of the test scores, with a greater improvement in VRTG, except for anxiety (HRS-A), whose improvement was similar in both groups.

Table 3: ANOVA decomposition in Group*Time for all tests/scales.

	Degree of freedom	Mean square	F	p value
MoCA	1, 98	100.82	242.76	**<0.001**
HRS-D	1, 98	129.60	54.45	**<0.001**
HRS-A	1, 98	88.44	40.76	**<0.001**
TMT-A	1, 98	883.42	17.35	**<0.001**
TMT-B	1, 98	20555.60	56.78	**<0.001**
TMT B-A	1, 98	7082.28	21.21	**<0.001**
VS	1, 98	571.119	43.72	**<0.001**
FAB	1, 98	52.92	60.61	**<0.001**
WEIGL	1, 98	86.39	69.28	**<0.001**

Significant p values are in bold. Legend: FAB: Frontal Assessment Battery; HRS-A: Hamilton Rating Scale for Anxiety; HRS-D: Hamilton Rating Scale for Depression; MoCA: Montreal Cognitive Assessment; TMT-A: Trail Making Test—Form A; TMT-B: Trail Making Test—Form B; TMT B-A: Trail Making Test—Form B-A; VS: Visual Search; WEIGL: Weigl Test.

4. Discussion

Our data confirm that VRT may be effective in the recovery of patients with TBI. In fact, although both groups achieved significant improvements in different cognitive and mood domains, patients undergoing VRT obtained better results. Moreover, only VRTG improved in specific cognitive domains, such as cognitive flexibility, attentional shifting, visual search, and executive and visuospatial functions, that are necessary for planning and managing daily life. Thus, VR can be considered a useful tool for patients with TBI, as demonstrated in various neurological disorders by previous studies [28–33]. Indeed, it has been shown that VRT is effective in enhancing attention, visual-spatial capacity, and motor function in patients with stroke [28, 29]. Doniger et al. showed that VR is a useful tool in cognitive and motor rehabilitation of patients with Alzheimer's disease [30]. These positive results were also confirmed in patients with multiple sclerosis, as 2D VR was able to further boost neural plasticity and thus functional recovery [31]. A recent pilot study performed on individuals with Parkinson's disease found that VR improved cognitive functions, with regard to executive and visuospatial domains, besides mood [32]. Finally, Maresca et al. observed significant improvements in different cognitive and motor domains as well as a reduction in anxiety and depressive symptoms in a patient affected by spinal cord injury [33]. Our data confirm these results, demonstrating that VRT can be effective also for patients with TBI. In our study, we used BTs-N, which creates a three-dimensional computer environment that can be explored using computer devices, projecting the user into a realistic scenario. This experience promotes the whole involvement of the patient, as the increased feedback may induce major

Table 4: Post hoc analysis of clinical scores between baseline (T0) and follow-up (T1), for both the Virtual Reality Training Group (VRTG) and the Traditional Cognitive Rehabilitation Group (TCRG).

Clinical assessment	VRTG		p value	TCRG		p value
	T0	T1		T0	T1	
MoCA	23.0 (21.25–24.7)	27.0 (26.0–28.0)	**<0.001**	23.0 (20.0-24.7)	24.0 (22.0-25.7)	**<0.001**
HRS-D	10.0 (6–13.7)	5.0 (3.0–7.0)	**<0.001**	12.0 (7.25-13.0)	10.0 (6.25-12.0)	**<0.001**
HRS-A	10.0 (4.25–13.7)	6.0 (1.0–8.7)	**<0.001**	9.0 (5.25-11.7)	7.0 (5.0-10.0)	**<0.001**
TMT-A	67.5 (55.25-100)	57.0 (35.0–88.0)	**<0.001**	79.5 (57.25-168.0)	74.5 (55.0-160.75)	**<0.001**
TMT-B	201.5 (130.2–274.0)	145.5 (92.0–200.0)	**<0.001**	179.0 (140.0-246.5)	174.0 (140.0-237.5)	**<0.001**
TMT B-A	95.5 (57.5–161.0)	82.5 (40.0–115.5)	**<0.001**	82.0 (65.0-160.5)	80.5 (62.5-155.0)	0.4
VS	34.0 (26.0–43.7)	42.7 (36.8–47.2)	**<0.001**	33.6 (25.1-43.7)	36.8 (27.1-46.2)	**0.002**
FAB	14.4 (11.1–15.9)	17.2 (15.2–18.0)	**<0.001**	13.6 (13.0-16.3)	14.9 (14.0-16.4)	**<0.001**
WEIGL	8.1 (6.3–9.2)	12.1 (10.1–14.0)	**<0.001**	7.2 (4.7-10.7)	8.2 (5.8-11.5)	**<0.001**

Scores are in median (first-third quartile); significant differences are in bold. Legend: FAB: Frontal Assessment Battery; HRS-A: Hamilton Rating Scale for Anxiety; HRS-D: Hamilton Rating Scale for Depression; MoCA: Montreal Cognitive Assessment; TMT-A: Trail Making Test—Form A; TMT-B: Trail Making Test—Form B; TMT B-A: Trail Making Test—Form B-A; VS: Visual Search; WEIGL: Weigl Test.

changes in neuronal plasticity that are responsible for restoring motor activity and/or cognitive function, thanks to the so-called "reinforcement learning" [28]. This leads us to believe that VRTG registered better results because VR may have boosted the neural plasticity processes and thus the functional recovery, as compared to the traditional therapies. In fact, it is well known that physical and cognitive exercise can increase the process of brain repair and plasticity after injuries, and the recovery is better, more intensive, repetitive, and task-oriented [34, 35]. The brain areas most often involved in TBI are the frontal and temporal lobes, especially in the basal areas and the subcortical white matter, leading to attention deficit, learning and memory, affect and expression, problem solving abilities, and executive function with a significant impact on the quality of life of the patient and his/her family [5, 6]. Therefore, VRT, thanks to the multisensory approach, can stimulate and enhance the spontaneous post-TBI regeneration processes, which otherwise may be short-lived and too weak to counter the deterioration of damage [36]. In fact, the exercises performed in a virtual environment help the patient to develop the knowledge of the results of the movements (knowledge of the results) and the knowledge of the quality of the movements (knowledge of the performances), which positively affect patient's functional recovery, including the cognitive one [28]. Thus, VR could allow greater results than paper-pencil exercises, through global stimulation and dual cognitive and motor tasking, which allow greater patient involvement. Indeed, according to Dahdah et al. [20], our data demonstrate, for the first time ever, that semi-immersive VR may be effective in improving executive functions and the speed of information processing in patients with TBI. Furthermore, VR increases motivation and enjoyment of the patients (important factors for successful rehabilitation), further favoring the behavioral and cognitive recovery, as also observed by Dvorkin et al. [37].

The main limitation of the study is the absence of a control group without a cognitive treatment, to exclude the case that patients' mood, anxiety, and some aspects of cognition improved due to recovery independent of the interventions. Nonetheless, this study design is difficult to perform, as CR is becoming the standard treatment of neurological patients.

5. Conclusions

This study suggests that semi-immersive VR using BTs-N may be a useful approach for the rehabilitation of individuals with TBI, potentially leading to better cognitive and behavioral outcomes. Further studies are needed, to confirm our promising results and to assess whether and to what extent VR cognitive training can improve overall functional recovery and quality of life in TBI patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors' Contributions

Rosaria De Luca and Maria Grazia Maggio equally contributed to the work.

References

[1] D. K. Menon, K. Schwab, D. W. Wright, A. I. Maas, and Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health, "Position statement: definition of traumatic brain injury," *Archives of Physical Medicine and Rehabilitation*, vol. 91, no. 11, pp. 1637–1640, 2010.

[2] K. Hackenberg and A. Unterberg, "Traumatic brain injury," *Der Nervenarzt*, vol. 87, no. 2, pp. 203–216, 2016.

[3] C. Iaccarino, A. Carretta, F. Nicolosi, and C. Morselli, "Epidemiology of severe traumatic brain injury," *Journal of Neurosurgical Sciences*, vol. 62, no. 5, pp. 535–541, 2018.

[4] S. Yamamoto, H. S. Levin, and D. S. Prough, "Mild, moderate and severe: terminology implications for clinical and experimental traumatic brain injury," *Current Opinion in Neurology*, vol. 31, no. 6, pp. 672–680, 2018.

[5] D. Latella, M. G. Maggio, R. de Luca et al., "Changes in sexual functioning following traumatic brain injury: an overview on a neglected issue," *Journal of Clinical Neuroscience*, vol. 58, pp. 1–6, 2018.

[6] M. G. Maggio, R. de Luca, M. Torrisi et al., "Is there a correlation between family functioning and functional recovery in patients with acquired brain injury? An exploratory study," *Applied Nursing Research*, vol. 41, pp. 11–14, 2018.

[7] J. K. Werner and R. D. Stevens, "Traumatic brain injury: recent advances in plasticity and regeneration," *Current Opinion in Neurology*, vol. 28, no. 6, pp. 565–573, 2015.

[8] V. Galetto and K. Sacco, "Neuroplastic changes induced by cognitive rehabilitation in traumatic brain injury: a review," *Neurorehabilitation and Neural Repair*, vol. 31, no. 9, pp. 800–813, 2017.

[9] M. G. Maggio, R. de Luca, F. Molonia et al., "Cognitive rehabilitation in patients with traumatic brain injury: a narrative review on the emerging use of virtual reality," *Journal of Clinical Neuroscience*, vol. 61, pp. 1–4, 2019.

[10] N. Robitaille, P. L. Jackson, L. J. Hébert et al., "A Virtual Reality avatar interaction (VRai) platform to assess residual executive dysfunction in active military personnel with previous mild traumatic brain injury: proof of concept," *Disability and Rehabilitation: Assistive Technology*, vol. 12, no. 7, pp. 758–764, 2017.

[11] E. Pietrzak, S. Pullman, and A. McGuire, "Using virtual reality and videogames for traumatic brain injury rehabilitation: a structured literature review," *Games for Health Journal*, vol. 3, no. 4, pp. 202–214, 2014.

[12] A. Barman, A. Chatterjee, and R. Bhide, "Cognitive impairment and rehabilitation strategies after traumatic brain injury," *Indian Journal of Psychological Medicine*, vol. 38, no. 3, pp. 172–181, 2016.

[13] J. Aida, B. Chau, and J. Dunn, "Immersive virtual reality in traumatic brain injury rehabilitation: a literature review," *NeuroRehabilitation*, vol. 42, no. 4, pp. 441–448, 2018.

[14] M. Jacoby, S. Averbuch, Y. Sacher, N. Katz, P. L. Weiss, and R. Kizony, "Effectiveness of executive functions training within a virtual supermarket for adults with traumatic brain injury: a pilot study," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 21, no. 2, pp. 182–190, 2013.

[15] J. M. Martínez-Moreno, P. Sánchez-González, M. Luna, T. Roig, J. M. Tormos, and E. J. Gómez, "Modelling ecological cognitive rehabilitation therapies for building virtual environments in brain injury," *Methods of Information in Medicine*, vol. 55, no. 1, pp. 50–59, 2016.

[16] S. Manivannan, M. Al-Amri, M. Postans, L. J. Westacott, W. Gray, and M. Zaben, "The effectiveness of virtual reality interventions for improvement of neurocognitive performance after traumatic brain injury: a systematic review," *The Journal of Head Trauma Rehabilitation*, vol. 34, no. 2, pp. E52–E65, 2019.

[17] S. H. A. Chen, J. D. Thomas, R. L. Glueckauf, and O. L. Bracy, "The effectiveness of computer-assisted cognitive rehabilitation for persons with traumatic brain injury," *Brain Injury*, vol. 11, no. 3, pp. 197–210, 1997.

[18] M. G. Maggio, R. de Luca, G. Maresca et al., "Personal computer-based cognitive training in Parkinson's disease: a case study," *Psychogeriatrics*, vol. 18, no. 5, pp. 427–429, 2018.

[19] R. De Luca, S. Leonardi, L. Spadaro et al., "Improving cognitive function in patients with stroke: can computerized training be the future?," *Journal of Stroke and Cerebrovascular Diseases*, vol. 27, no. 4, pp. 1055–1060, 2018.

[20] M. N. Dahdah, M. Bennett, P. Prajapati, T. D. Parsons, E. Sullivan, and S. Driver, "Application of virtual environments in a multi-disciplinary day neurorehabilitation program to improve executive functioning using the Stroop task," *NeuroRehabilitation*, vol. 41, no. 4, pp. 721–734, 2017.

[21] Z. S. Nasreddine, N. A. Phillips, V. Ã.©. BÃ©dirian et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[22] M. Hamilton, "A rating scale for depression," *Journal of Neurology, Neurosurgery, & Psychiatry*, vol. 23, no. 1, pp. 56–62, 1960.

[23] M. Hamilton, "The assessment of anxiety states by rating," *British Journal of Medical Psychology*, vol. 32, no. 1, pp. 50–55, 1959.

[24] B. Dubois, A. Slachevsky, I. Litvan, and B. Pillon, "The FAB: a frontal assessment battery at bedside," *Neurology*, vol. 55, no. 11, pp. 1621–1626, 2000.

[25] M. G. Inzaghi, *Test di Weigl, Manuale*, Giunti O.S. Organizzazioni Speciali, 2010.

[26] H. Spinnler and G. Tognoni, "Standardizzazzione e taratura Italiana di test neuropsicologici," *The Italian Journal of Neurological Sciences*, vol. 6, no. 8, pp. 21–120, 1987.

[27] R. M. Reitan, "Validity of the Trail Making test as an indicator of organic brain damage," *Perceptual and Motor Skills*, vol. 8, no. 3, pp. 271–276, 1958.

[28] R. De Luca, M. Russo, A. Naro et al., "Effects of virtual reality-based training with BTs-Nirvana on functional recovery in stroke patients: preliminary considerations," *International Journal of Neuroscience*, vol. 128, no. 9, pp. 791–796, 2018.

[29] M. G. Maggio, D. Latella, G. Maresca et al., "Virtual reality and cognitive rehabilitation in people with stroke: an overview," *Journal of Neuroscience Nursing*, vol. 51, no. 2, pp. 101–105, 2019.

[30] G. M. Doniger, M. S. Beeri, A. Bahar-Fuchs et al., "Virtual reality-based cognitive-motor training for middle-aged adults at high Alzheimer's disease risk: a randomized controlled trial," *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, vol. 4, pp. 118–129, 2018.

[31] M. Russo, V. Dattola, M. C. de Cola et al., "The role of robotic gait training coupled with virtual reality in boosting the rehabilitative outcomes in patients with multiple sclerosis," *International Journal of Rehabilitation Research*, vol. 41, no. 2, pp. 166–172, 2018.

[32] M. G. Maggio, M. C. de Cola, D. Latella et al., "What about the role of virtual reality in Parkinson disease's cognitive rehabilitation? Preliminary findings from a randomized clinical trial," *Journal of Geriatric Psychiatry and Neurology*, vol. 31, no. 6, pp. 312–318, 2018.

[33] G. Maresca, M. G. Maggio, A. Buda et al., "A novel use of virtual reality in the treatment of cognitive and motor deficit in

spinal cord injury: a case report," *Medicine*, vol. 97, no. 50, article e13559, 2018.

[34] A. Sale, N. Berardi, and L. Maffei, "Enrich the environment to empower the brain," *Trends in Neurosciences*, vol. 32, no. 4, pp. 233–239, 2009.

[35] R. S. Calabrò, A. Naro, M. Russo et al., "The role of virtual reality in improving motor performance as revealed by EEG: a randomized clinical trial," *Journal of Neuroengineering and Rehabilitation*, vol. 14, no. 1, p. 53, 2017.

[36] A. I. R. Maas, D. K. Menon, P. D. Adelson et al., "Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research," *The Lancet Neurology*, vol. 16, no. 12, pp. 987–1048, 2017.

[37] A. Y. Dvorkin, M. Ramaiya, E. B. Larson et al., "A "virtually minimal" visuo-haptic training of attention in severe traumatic brain injury," *Journal of Neuroengineering and Rehabilitation*, vol. 10, no. 1, p. 92, 2013.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 9785319, 17 pages
https://doi.org/10.1155/2019/9785319

Research Article

Effects of Systematic Categorization Training on Cognitive Performance in Healthy Older Adults and in Adults with Traumatic Brain Injury

Fofi Constantinidou

Department of Psychology and Center for Applied Neuroscience, University of Cyprus, Nicosia, Cyprus

Correspondence should be addressed to Fofi Constantinidou; fofic@ucy.ac.cy

Received 13 March 2019; Accepted 11 June 2019; Published 29 July 2019

Guest Editor: Lambros Messinis

Copyright © 2019 Fofi Constantinidou. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This study investigated the effects of hierarchical cognitive training using the categorization program (CP), designed initially for adults with cognitive deficits associated with traumatic brain injury (TBI). Fifty-eight participants were included: a group of fifteen young adults with TBI (ages 18-48), another group of fifteen noninjured young adults (ages 18-50), and two groups of adults over 60 randomly assigned into the experimental group ($n = 14$) or the control group ($n = 14$). Following neuropsychological testing, the two young adult groups and the experimental older adult group received the CP training for 10-12 weeks. The CP training consisted of 8 levels targeting concept formation, object categorization, and decision-making abilities. Two CP tests (administered before and after the training) and three probe tasks (administered at specified intervals during the training) assessed skills relating to categorization. All treated groups showed significant improvement in their categorization performance, although younger participants (with or without TBI) demonstrated greater gains. Gains on the categorization measures were maintained by a subgroup of older adults up to four months posttraining. Implications of these findings in terms of adult cognitive learning and directions for future research on adult cognitive rehabilitation and cognitive stimulation programs are discussed.

1. Introduction

Several studies demonstrated that older adults benefit from cognitive training efforts that target specific processes. These findings create a paradigm shift because they suggest that the aging brain continues to be somewhat plastic and adaptable in old age. Improvement associated with training could be attributed to the development of a new skill or the facilitation of existing cognitive mechanisms and capacities [1, 2] that may be affected due to the aging process. Ultimately, cognitive training in aging could contribute to the increase of cognitive reserve, the brain's ability to withstand pathology [3].

Age-related cognitive changes are generally highly heterogeneous and are typically noted in tasks with high demands on speed of information processing and executive control (such as complex working memory tasks requiring manipulation of information), as compared to simple or automatic tasks (such as digit recall tasks) [3–6]. These changes in episodic memory can be measurable starting at age 30, and the rate of age-related decline in verbal episodic memory is normally mediated by working memory capacity [7]. The goal of cognitive training is to reduce the impact of the aging process on the cognitive system, [8] and in order to be successful, training programs should be based on sound theoretical models of cognition.

Contemporary cognitive theory organizes human cognition into a hierarchy of basic and complex processes or systems. Basic processes such as sensory perception, attention, and memory underlie more complex systems such as language, categorization, and executive functioning (for an extensive review, refer to Constantinidou and Thomas [9]). Deficits in categorization could interfere with the successful execution of daily activities because categorization skills are integral to memory and learning of new information and are essential processes for decision-making and successful problem-solving. Given the fundamental importance of

categorization to all of intelligent behavior, it is surprising to observe the scarcity of investigation specific to the effects of aging on classification behavior. This is in contrast to other domains such as speed of processing and memory for which a substantial body of work can be found [10, 11]. The current study proposes to fill some of this gap in knowledge and is part of a systematic research program on the effects of categorization training on cognitive performance. Our previous research suggests that the CP is effective in young adults with TBI [12, 13]. The next paragraphs provide the theoretical framework for categorization-classification behavior relevant to this study.

The literature on categorization, especially that which is focused on visual object classification, divides into two largely nonoverlapping areas: those studies concerned with how we go about recognizing and categorizing ordinary objects in the world [14, 15] and those studies whose purpose is primarily to explain how novel situations or categories are acquired and later used to classify novel instances [16–18].

Regarding object perception, recognition, and categorization, semantic knowledge models support a bilateral temporal lobe hub which links object properties and conceptual understanding [19]. Furthermore, evidence in vision indicates the presence of a hierarchical recognition process that begins with early feature processing (such as orientation, motion, and color) and leads to the processing and representation of objects and object classes in the inferotemporal cortex [15, 20, 21]. Existing research suggests that both healthy aging and TBI result in changes in object classification [22, 23], indicating that treatment of object classification behavior should begin with feature identification in order to retrain the passive object recognition system [9].

For new category learning and classification of novel instance, empirical evidence suggests that people recruit one of two explicit systems (i.e., their processes and outputs are consciously available to the individual). The rule-based or rule-governed category system is the most important of the two. It involves the use of explicit verbalizable rules and hypothesis testing to determine category membership. This system relies heavily on executive functioning for its operation and engages frontal-subcortical networks. The other explicit system that requires significant episodic memory in that categorization is accomplished by the recall of previously experienced category members, or exemplars, that are similar to the present novel object [9, 17]. This latter system works by evaluating similarity, in terms of object or situation features, of to-be-categorized instances to those encountered previously [24], and its operation is sometimes labeled as procedural or nonexplicit, in the sense that one cannot easily describe the strategy used. Our knowledge of natural categories and common objects is likely to have been acquired through the use of the similarity-based system [20, 21, 25]. A long list of neuropsychological and experimental studies supports the above distinction [26–30]. The categorization program implemented in this study is organized hierarchically in order to address these two distinct areas of classification.

While the process of healthy aging is different from the pathology of TBI, healthy aging results in changes in categorization abilities, similar to TBI [22, 23]. Even though higher levels of cognitive reserve result in improved neurocognitive performance and moderate the effects of aging, age continues to be a robust predictor of neurocognitive functioning [3, 31].

Both TBI and age have been established as significant risk factors for the development of pathological aging resulting in dementia. TBI is now viewed as a chronic condition, and there is accumulating evidence suggesting that TBI and dementia of the Alzheimer's type share a common neuropathologic sequelae, such as chronic neuroinflammation (see review by Breunig et al. [32]), tauopathy [33], and the accumulation of beta amyloid (Aβ) [34], leading to significant neurocognitive impairment. Moderate-severe TBI sets off a neurodegenerative cascade as manifested by significant reductions in brain volume and lingering neurocognitive deficits [35] associated with longer time since injury placing the survivor at risk for dementia in middle/later life [36].

The current project responds to the challenge set by the NIH consensus report on preventing AD and cognitive decline [37]. The primary objective of this project was to investigate the utility of intense neurocognitive training in healthy older adults who experience neurocognitive changes associated with the normal aging process, using the categorization program (CP). A secondary objective was to compare the performance of older adults to younger healthy adults and to adults with cognitive deficits secondary to brain injury. Results from this study could guide future research investigating the effects of intense neurocognitive training on older adults with TBI and adults with mild cognitive impairment, the prodromal phase to dementia.

The CP is a rigorous systematic, hierarchical, eight-level program initially designed as a restorative cognitive rehabilitation program in adults with acquired brain injury. It addresses the aforementioned two distinct areas of human categorization, i.e., passive object recognition and new category learning. Initial research findings [12] and a subsequent randomized controlled trial [13] indicate that the CP is an effective therapy tool for adults with brain injury who exhibit categorization deficits. Constantinidou et al. [13] offered the following explanations regarding the active ingredients of the CP:

(i) The CP addresses both aspects of categorization, novel category learning, and categorization of established concepts or categories. It incorporates concrete visual stimuli and gradually progresses into abstract concepts through the use of repetition, cueing, and strategy building

(ii) The CP was built using a very systematic hierarchical structure that corresponds to the neurodevelopmental order of categorization and classification process hierarchy

(iii) Tasks gradually increase in difficulty and cognitive abstraction. CP tasks begin with basic feature identification and feature extraction (such as color, shape, and size) and progress to higher levels of concept formation and abstraction (such as rule-based decision-making) [38, 39]

(iv) The program integrates cognitive processes such as executive skills, attention, organization, conceptual reasoning, linguistic flexibility, and explicit memory for the completion of the categorization tasks

(v) The redundancy and the repetition integrated in each level, along with the extensive cueing systems and errorless learning principles, provide support and organization for participants with more passive learning styles. The program provides a standardized approach to categorization training; yet, it incorporates mastery criteria for each level in order to account for individual differences. In conclusion, the CP targets cognitive domains such as complex working memory, information processing, and fluid intelligence that traditionally have been associated with age-related cognitive decline

The present study investigated categorization abilities and the effects of training on healthy older adults over 60 and in a group of young adults with moderate to severe TBI. In order to account for previous methodological flaws in adult training studies and determine the true effects of training, this study incorporated an older adult control group (who did not receive the training) and a young adult group who received training. The primary hypotheses were the following:

(1) All participants who receive the CP training would demonstrate improvements in their categorization performance as measured by gains on the CP-dependent measures

(2) Participants who receive the CP training would be able to generalize their knowledge to other categorization tasks not directly related to the CP, to a greater degree than participants who do not receive the CP training

(3) Performance of older adults on formal neuropsychological measures measuring memory, executive function, perception, conceptual reasoning, and attention would correlate significantly with performance on categorization tests

(4) Older adults who receive the CP training would be able to maintain their gains on categorization performance at one and four months posttraining

2. Materials and Methods

2.1. Participants. Fifty-eight participants were included in the study. One group consisted of young adults with TBI who received the CP training ($n = 15$), a second group of young healthy adults who also received the CP training ($n = 15$), a third group of healthy older adults who received the training ($n = 14$), and a fourth group of healthy older adults who did not receive the training ($n = 14$). Participants with TBI were recruited from brain injury rehabilitation centers collaborating in the project. The rest of the participants (groups 2-4) were volunteers from southwest Ohio areas. Recruitment of the TBI and noninjured groups was done in parallel and in a rolling admission process. All work was conducted in accordance with the Declaration of Helsinki (1964), and the project was approved by the Miami University Institutional Review Board for Human Subjects in Research. All study participants provided written informed consent prior to participation. Study participants were English-speaking adults and met the study's inclusion/exclusion criteria as follows.

2.2. Young Adults with TBI. The following are the inclusion/exclusion criteria for participants with TBI, which are consistent with the Constantinidou et al. [12] criteria.

2.2.1. Inclusion Criteria

(1) Adult males and females between 18 and 55 years of age

(2) Primary diagnosis of moderate to severe CHI. The indication of an initial moderate to severe head injury was determined by the presence of three or more of the following severity indices: (a) initial Glasgow Coma Scale score less than 12, (b) abnormal initial computed tomography (CT) findings indicating acute central nervous system pathology, (c) length of impaired consciousness greater than 20 minutes as specified by the emergency records, (d) length of posttraumatic amnesia greater than 24 hours as specified in the acute hospital/emergency records, (e) length of acute hospital stay greater than 3 days, (f) positive neurological examination on hospital admission and discharge indicating focal sensory and motor neurological deficits or changes in the mental status attributed to brain injury, (g) medical complications secondary to the injury, and (h) head injury severity classification according to hospital records [40, 41]

(3) Rancho Los Amigos Scale [42] Level VI or higher (which indicates appropriate, goal-oriented behavior and posttraumatic amnesia (PTA) resolution)

(4) No aphasia present with the exception of mild to moderate word-finding problems due to cognitive deficits

(5) Resolution of PTA as evidenced by a score of 76 or higher on the Galveston Orientation and Amnesia Test [43]

(6) Enrollment in a residential comprehensive postacute rehabilitation program at the onset of the study

(7) Participants were within 4 years of their injury

2.2.2. Exclusion Criteria

(1) Penetrating head injuries

(2) Diagnosis of stroke at the time of injury

(3) Premorbid central nervous system disorder or learning disability

(4) Documentation of premorbid major depression or other significant psychiatric disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] [44] that resulted in hospitalization and/or incapacity to work or perform activities of daily living

(5) Current Beck Depression II [45] score of 25 or higher indicating the presence of depression that could interfere with performance on the protocol. This score is higher than the typical cut-off score of 15 because as previously described [12], TBI results increased symptomatology for reasons relevant to TBI and not because of clinical depression. A score of 25 or higher indicates clinical depression in this population

(6) Active or current alcohol, drug, or other controlled substance abuse that interferes with participation

(7) Deficits in auditory comprehension and moderate to severe word-finding problems, two standard deviations below the mean on the Boston Naming Test [46], which could interfere with the subject's ability to follow test or task instructions

(8) English as a second language

(9) Color blindness as measured by the Ishihara test for color blindness [47]

Seventy percent of the participants were injured in motor vehicle accidents, and another 30% were injured as a result of falls. All participants received comprehensive rehabilitation at the time of participation in the project.

2.3. Noninjured Adult Groups

2.3.1. Inclusion Criteria

(1) Adult males and females between 18 and 55 years of age for the young adult group

(2) Adults over 60 for the older adult groups

2.3.2. Exclusion Criteria

(1) A medical history of a central nervous system trauma, disorder, or organic brain disease, learning disability, or language learning disability

(2) Documentation of psychological or psychiatric disorder as defined by the DSM-IV [44] that resulted in hospitalization for major depression and/or incapacity to work

(3) Current Beck Depression II [45] score of 15 or higher indicating the presence of depression that could interfere with performance on the protocol

(4) Mini-Mental State Examination score of 25 or lower [48]

(5) Active or current alcohol, drug, or other controlled substance abuse

(6) Uncorrected visual or hearing deficits

(7) Color blindness as measured by the Ishihara test for color blindness [47]

2.4. Group 1: Experimental Young Adult Group with TBI ($n = 15$). Participants were residents of postacute rehabilitation centers and were enrolled in the project through a rolling admission process. They remained in the study for an average of 10-12 weeks which coincided with their length of stay at the rehabilitation centers. Participants in this group ranged in age from 18 to 48 years with a mean age of 28.13 (SD = 9.21). Education ranged from 12 to 17 years, with a mean of 13.67 (SD = 1.78).

2.5. Group 2: Young Adult Group ($n = 15$). The ages of the participants ranged from 19 to 50 years with a mean age of 29.73 years (SD = 10.89). Education ranged from 12 to 18 years, with a mean of 14.16 (SD = 1.87).

2.6. Group 3: Experimental Older Adult Group ($n = 14$). Participants ranged in age from 60 to 82 years with a mean age of 67.28 years (SD = 10.47). Education ranged from 12 to 19 years, with a mean of 13.9 (SD = 2.15). Their average MMSE score was 28.5 (SD = 1.55).

2.7. Group 4: Older Adult Control Group ($n = 14$). Their ages ranged from 60 to 88 years with a mean age of 68.64 years (SD = 9.72). Education ranged from 10 to 18 years, with a mean of 13.92 (SD = 2.05). Their average MMSE score was 29.42 (SD = .85).

Healthy older adults who met the inclusion/exclusion criteria for the project were randomly assigned to either the experimental or the control group. The two older adult groups did not differ significantly in age or education level, $t(26) = .355$, $p = .725$ and $t(26) = .043$, $p = .966$. There was no difference in their gross cognitive ability as measured by the MMSE $t(26) = 1.958$, $p = .061$. Finally, there was no significant difference between the four groups on the years of education, $F(3, 54) = .154$, $p = .927$.

2.8. Procedures. Participants were administered a neuropsychological assessment at the beginning of their participation in the project. Following the neuropsychological testing, participants were administered two categorization tests designed for this project and the first probe task (see sections 2.11 and 2.12 for a description of the tests and probe tasks). All participants remained in the study for 10-12 weeks. Participants who received the CP training (groups 1, 2, and 3) participated in individualized hourly sessions for a total of 2-4 hours of training per week until they completed the CP protocol. On average, participants required 27 hours to complete the CP training. Table 1 displays the experimental design.

2.9. Experimental Items. The experimental items are consistent with the materials described previously [12, 13], and the description partly reproduces their wording:

Table 1: Experimental design.

	Pretests	Probe 1	Part A Perceptual feature training Level 1	Similarities and differences Level 2	Probe 2	Functional categorization Level 3	Analogies Level 4	Abstract concepts Level 5	Probe 3	Part B Levels 1-3	Posttests
Group 1: young adults with TBI (treated)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 2: young uninjured adults (treated)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 3: older adults (treated)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 4: older adults (untreated)	✓	✓			✓				✓	✓	✓

Note: pre/posttests include the neuropsychological assessment and the 2 tests of the categorization program. Probe 2 was inserted at about 5 weeks after the onset of treatment and probe 3 at 8 weeks for the control group.

2.10. The Categorization Program (CP). The CP was based on theories of implicit and explicit categorization systems. Therefore, tasks were grouped into two major parts: (1) recognition and categorization of everyday objects and (2) new category learning [12]. Principles of learning, concept formation, and rehabilitation were incorporated in order to develop the hierarchical tasks [49–52]. Table 2 presents the 8 levels of the CP.

2.10.1. Part A: Object Categorization Tasks. This part consists of 5 different levels. The tasks begin with teaching perceptual features in order to describe objects or living things and move to higher levels of cognition including analyses, synthesis, linguistic flexibility, and abstract reasoning.

2.10.2. Part B: New Category Learning Tasks. The new category learning tasks consist of three levels. Under each level, there are 5 steps that increasingly demand a higher level of rule-governed responses. Errorless learning principles and cueing hierarchies are applied under each step.

The CP-dependent measures were developed to measure the effectiveness of the CP program. These were the CP Test 1, CP Test 2, and probe tasks 1, 2, and 3.

2.11. CP Tests 1 and 2. CP Test 1 relates to the categorization of common objects (Part A of the CP). Participants were required to describe pictures of objects and identify core attributes such as their primary function and alternate uses of the object. These objects were not part of the CP training. There were a total of 10 objects; five have high frequency and five have low frequency in occurrence [53]. The number correctly obtained from 120 possible was recorded for each subject. Cronbach's alpha for the 10 items is .90.

The second test relates to the new category learning portion (Part B of the CP). Participants were required to follow a logical rule in categorizing objects. These objects were not part of the CP. There were a total of 5 rules with increased complexity. For instance, the first rule asks the subject to "put all red items in the basket." The last rule is more complex and requires that participants to "put all things that are blue but not used for coffee in the basket." Both informal tests were administered at the beginning and at the end of the study. The number correctly obtained from 36 possible was recorded for each subject. Cronbach's alpha for CP Test 2 was .69.

2.12. CP Probe Tasks. The probe tasks were designed to assess how participants generalize information learned on the CP to other tasks not directly related to the CP training tasks. Participants were presented with an array of 10 objects and were required to categorize objects based on a self-generated rule. Following that, they were asked to categorize the same objects twice, each time using a different self-generated rule.

The probe tasks were administered at 3 different times during the study. The first probe task was administered prior to the CP training, the second after Level 2 (Part A), and the third after Level 5 (Part A). For the treated control group participants, the first probe was administered prior to the onset of therapy, the second after 5 weeks of treatment, and the third after 8 weeks of treatment. Each of the probe task uses a set of 10 different objects, equal in familiarity and frequency of occurrence. The three different sets of probe tasks are of similar difficulty, and analyses of variance yielded no statistical difference in performance ($p > .05$) between the three different sets of items. The order of administration was counterbalanced to avoid order effects. Participants obtained one point for each object they sorted correctly by their self-generated rule. The subject was asked to sort the items three times under each probe task, each time using a different rule. Hence, each probe trial was worth 10 points with a total of 30 points for each probe task.

2.13. CP Stimuli and Scoring System. The CP protocol was provided in a manualized format in order to ensure consistency. The CP packet included the administration manual with cueing instructions, the CP stimuli (objects, photos, written words, etc.), and score sheets.

2.14. Neuropsychological Tests. The following tests were administered at pre- and posttesting.

(i) Wechsler Abbreviated Scale of Intelligence (WASI) [54]

(ii) Mini-Mental State Examination [55]

(iii) Rey Complex Figure Test [56]

(iv) Trail Making Tests A and B [57]

(v) Digit Span Forward and Backwards and Visual Span Forward and Backwards—*Wechsler Memory Scale-III* (WMS-III) [58]

(vi) California Verbal Learning Test-II [59]

(vii) Wisconsin Card Sorting Test [60]

(viii) The Booklet Category Test [61]

(ix) Symbol Digit Modalities Test [62]

(x) Control Oral Word Association [63]

(xi) The Picture Recognition, Spatial Relations, Analysis and Synthesis, Concept Formation, Decision Speed, and Verbal Comprehension Subtests from the Woodcock-Johnson III (WJIII, Tests of Cognitive Abilities) [64]

2.15. Data Scoring and Analyses. Data were included in the analyses to the fullest extent possible. The primary statistical design was a multivariate mixed model design followed by preplanned univariate comparisons. The alpha level was set at .05.

3. Results

Participants who received the CP protocol required about 27 hours of treatment spread over 10-12 weeks. The participants in the control group did not receive any cognitive treatment other than information regarding memory strategies and a list of suggested activities for cognitive stimulation.

Table 2: The eight levels of the categorization program (adapted from Constantinidou et al. [38] and Constantinidou et al. [12]).

Part A: object categorization tasks	This part consists of 5 different levels. The tasks begin with teaching perceptual features in order to describe objects or living things and move to higher levels of abstraction.
Level 1: perceptual feature training and application	The purpose of this section is to train perceptual feature identification thereby building a framework for cognitive structures. The retraining of basic categorization abilities will build the foundation for more abstract functions and will facilitate communication during word-finding difficulties. The patient will learn eight perceptual features and then consistently apply all the features to describe common objects. Objects are presented via a range of stimulus types including real objects, color photos, line drawings, written words, and spoken words.
Level 2: similarities and differences	The purpose of this level is to apply the eight perceptual features trained in Level 1 to compare objects. Identification of similarities and differences between two objects of the same and of different categories using the eight perceptual features is utilized in order to train conceptual thinking. The process of applying the trained perceptual features is the next layer of the continuum of concrete to abstract functional abilities. Stimulus types include colored photos, written words, and spoken words.
Level 3: functional categorization	The purpose of this task is to identify functional categories and maintain the delineations within that category. There are two specific foci in this level which require the consideration of the features of the objects trained and applied in Levels 1 and 2: the application of retrieval strategies to generate novel items that belong in a given category and the mental flexibility required to generate alternate uses for the objects in a given category. This task enhances functional problem-solving and mental flexibility.
Level 4: analogies	The purpose of this level is to apply both the categorization abilities trained in Levels 1-3 and inductive reasoning skills in order to identify and match the concepts represented in analogies. The analogies progress from concrete to abstract in order to train word abstraction. Stimulus materials include multiple choice responses for each analogy that will aid in the training process of word abstraction as needed.
Level 5: abstract word categorization	This level further develops concept formation and abstract conceptual thinking. The goal is to identify similarities and differences in abstract verbal concepts. The generation of similar word pairs using synonyms that represent the relationship between the words is incorporated to enhance cognitive and linguistic flexibility.
Part B: new category learning tasks	Under each level of the new category learning, there are 5 steps that increasingly demand a higher level of rule-governed responses. Errorless learning principles and cueing hierarchies are applied under each step.
Level 1: progressive rule learning 1	The stimuli for Level 1 vary along two dimensions: shape and color. The nine stimuli include squares, circles, and triangles that are red, white, and black. Each stimulus is presented individually, and a formulation of the rule that classifies each stimulus into either Category A or Category B follows.
Level 2: progressive rule learning 2	The stimuli for Level 2 of Part B are gauges that include two dials that must be interpreted as a single unit. This level forces generalization into a real world situation by simulating the reading of gauges at a power plant. The determination of operational or not operational for each stimulus is utilized, and the cumulative interpretation of each judgment leads to the formulation of the rule that classifies the stimuli for each of the five conditions.
Level 3: progressive rule learning 3	The final explicit rule task contains the same underlying structure as the earlier two levels; however, this time, a judgment is made using stimuli constructed from dimensions of language. This further abstracts the rule formulation and forces generalization of training to a real world situation. The stimuli in this task consist of a summary of three laboratory tests (lung capacity, heart fluid, and bone marrow count) and their orthogonal combination with two measurement adjectives (low and high).

3.1. Performance on CP Measures. CP measures consisted of the CP Test 1 (pre and post), CP Test 2 (pre and post), and the three probe tasks (Probe 1, Probe 2, and Probe 3).

3.1.1. CP Test 1. The first CP test assessed the ability to categorize common objects. In order to determine the effects of the CP training on categorizing familiar objects, a mixed model analyses of variance ($a = .05$) compared the pre- and postperformance of the four groups on the CP Test 1 with time (pre/post) as the within-subjects factor and group as the between-subjects factor. The analyses revealed a significant time effect ($F(1, 54) = 146.14$, $p = .0001$, $\eta\rho^2 = .730$, power = 1.000), group by time interaction ($F(3, 54) = 24.72$, $p = .0001$, $\eta\rho^2 = .579$, power = 1.0), and an overall group effect ($F(3, 54) = 11.411$, $p = .0001$, $\eta\rho^2 = .388$, power = .999).

Planned lower-order ANOVAs indicated that there was an overall group difference on the CP Test 1 baseline performance ($F(3, 57) = 6.026$, $p = .001$). However, there was no

Figure 1: CP Test 1 interaction and pre-post group effects.

difference at the baseline among the three healthy groups on CP Test 1 accuracy ($F(2, 42) = .187$, $p = .831$). Post hoc pairwise Bonferroni comparisons indicated that the baseline difference at CP Test 1 was due to the lower performance of the young group with TBI. Participants with TBI performed significantly lower on CP Test 1 at the baseline as compared to the healthy young adults and the two older adult groups.

At Time 2, there was a significant group main effect ($F(3, 54) = 19.785$, $p = .0001$). Post hoc pairwise Bonferroni comparisons revealed no difference between the TBI and the healthy young adult or the TBI and the older experimental group at Time 2. However, healthy young adults performed significantly better than their older counterparts who received the CP training. The older untreated group had the lowest performance among all groups at Time 2, and their performance was significantly lower than that of participants in the other groups (e.g., TBI, young adult, and older experimental groups). While all *treated* groups demonstrated significant growth from Time 1 to Time 2, the young adults (TBI and healthy young adults) demonstrated the most significant growth as compared to the older treated group, $t(27) = 3.585$, $p = .001$ and $t(27) = 3.576$, $p = .001$. The degree of improvement on CP Test 1 (i.e., difference score between pre-post performance) between the two young adult groups was similar ($t(28) = .209$, $p = .836$). Figure 1 displays time by group interaction depicting the change in performance from Time 1 to Time 2 on the CP Test 1 tasks. Table 3 presents the performance of each group on the CP-dependent measures.

3.1.2. CP Test 2. The second CP test assessed the ability to implement logical rules to categorize objects consistent with theories of category learning. In order to determine the effects of the CP training on implementing logical rules, a mixed model analyses of variance ($a = .05$) compared the pre- and postperformance of the four groups on the CP Test 2 with time (pre/post) as the within-subjects factor and group as the between-subjects factor. There was a time main effect ($F(1, 53) = 13.521$, $p = .001$, $\eta\rho^2 = .203$, power = .950) and a group main effect ($F(3, 53) = 4.830$, $p = .005$, $\eta\rho^2 = .215$, $p = .883$). The group by time interaction was not significant ($F(3, 53) = .756$, $p = .524$, $\eta\rho^2 = .041$, power = .201). Results indicate that the patterns of performance were similar among the groups. Planned lower-order ANOVAs indicated that there was a difference at the baseline between the four groups ($F(3, 53) = 2.964$, $p = .040$). The only significant difference was between the noninjured young adults and the two older adult groups ($F(2, 41) = 4.086$, $p = .024$). There were no other significant group differences at the baseline.

At Time 2, there was a significant group simple main effect ($F(3, 54) = 5.223$, $p = .003$). A priori pairwise comparisons ($\alpha = .01$) revealed significant differences between the young TBI group and the treated older adult group ($t(27) = 2.814$, $p = .009$) and between the healthy young adult group and the treated older adult group and untreated older adult groups ($t(27) = 2.839$, $p = .009$ and $t(27) = 2.78$, $p = .010$, respectively). Figure 2 displays group performance on the CP Test 2.

3.2. Probe Tasks. The probe tasks were designed to assess the participants' ability to implement skills learned during the CP training and categorize new objects. The three probe tasks were administered at three different intervals: before the CP training, after Level 2 (at 5 weeks after the onset of treatment), and after Level 5 (at 8 weeks after the onset of treatment). Participants in the control group received the probes before the onset of the study (i.e., baseline), at 5 weeks, and at 8 weeks.

A mixed model analysis of variance was performed with probe as the within-subjects factor and groups as the between-subjects factor. There was a significant probe effect ($F(2, 51) = 8.536$, $p = .001$, $\eta\rho^2 = .251$, power = .958), group by probe interaction ($F(6, 104) = 2.422$, $p = .032$, $\eta\rho^2 = .127$, power = .801), and a significant group main effect ($F(3, 52) = 3.238$, $p = .029$, $\eta\rho^2 = .158$, power = .715).

Pairwise analyses (mean difference estimations, $a = .01$) indicate that there was a significant improvement between the first and second probe administrations ($p = .001$). There was also a significant difference between the first and third probes ($p = .0001$). However, there was no significant difference between the second and third probes ($p = .291$).

The groups demonstrated different patterns on performance on the probe tasks. The greatest gain in performance was obtained by the young adult group with TBI ($F(2, 13) = 7.734$, $p = .006$, $\eta\rho^2 = .543$, power = .887). The performance of young adults with TBI and older adults during Probe 1 was more variable (compared to younger adults). However, their performance during Probes 2 and 3 became more uniformed. The performance of the young adult group was fairly stable across the three probes, probably due to a ceiling effect. Figure 3 displays group performance on the probe task across time.

Table 3: Mean (standard deviations) for CP Tests 1 and 2 and the probe tasks.

	CP Test 1		CP Test 2		Probes		
	Pre	Post	Pre	Post	Probe 1	Probe 2	Probe 3
Group 1: young adults with TBI (treated) ($n = 15$)	59.13 (9.47)	94.26 (17.91)	29.26 (3.82)	32.46 (2.29)	22.26 (7.59)	27.8 (4.07)	29.86 (.51)
Group 2: young uninjured adults (treated) ($n = 15$)	70.13 (8.77)	104.21 (14.75)	31.06 (3.39)	32.93 (3.43)	29.64 (.84)	29.33 (.25)	29.78 (.57)
Group 3: older adults (treated) ($n = 14$)	69.0 (7.93)	84.21 (12.02)	27.07 (4.40)	28.35 (5.13)	25.78 (6.11)	29.28 (2.67)	28.57 (3.63)
Group 4: older adults untreated ($n = 14$)	68.50 (4.76)	67.50 (3.67)	27.28 (4.81)	28.28 (5.41)	26.71 (6.0)	28.5 (2.67)	29.28 (2.67)

Note: the maximum possible score on CP Test 1 is 120, and on CP Test 2 is 36. The total number of possible points for each probe task is 30.

Figure 2: CP Test 2 pre-post group effects.

Figure 3: Probe effects per group across time.

3.3. Follow-Up Effects of CP Training. Out of the 14 older participants who received the CP training, 9 participants were able to complete follow-up assessments at one month and at 4 months after study completion in order to determine possible long-term effects of the CP training. The remaining five dropped out because they missed one of the two follow-up sessions due to illness, planned surgeries, death in the family, and travel. A repeated measures ANOVA ($a = .05$) on the CP Test 1 scores obtained during the four different administration times (pretest, posttest, follow-up Time 1, and follow-up Time 2) revealed significant differences in performance ($F(3, 24) = 11.69$, $p = .001$, $\eta\rho^2 = .593$, power = .0001). Preplanned Helmert contrasts indicated a significant difference in performance between the pretest score ($x = 72.11$, SD = 4.85) and the rest of the posttest scores ($F(1, 8) = 16.94$, $p = .002$, $\eta\rho^2 = .679$, power = .948) (posttest average score = 87.11, SD = 12.91; one – month average score = 95.56, SD = 17.16; and four – month average score = 92.33, SD = 16.04). There was no significant difference between the three posttest scores on CP 1 ($F(2, 7) = 3.832$, $p = .075$, $\eta\rho^2 = .523$, power = .499).

Similar to the CP Test 1, a repeated measures ANOVA ($a = .05$) on the CP Test 2 scores obtained over four different administration times (pretest, posttest, follow-up Time 1, and follow-up Time 2) revealed a significant overall effect ($F(3, 24) = 4.44$, $p = .013$, $d = .357$, power = .816). There was no significant difference between the three posttest scores on CP Test 2 ($F(2, 7) = 1.581$, $p = .271$, $\eta\rho^2 = .311$, power = .231) (posttest average score = 28.38, SD = 5.13; one – month average score = 30.33, SD = 3.96; and four – month average score = 30.33, SD = 5.26). In summary, the small group of participants who received the follow-up testing maintained their gains on CP Tests 1 and 2 after the training up to 4 months after the study completion.

3.4. Pretest Neuropsychological Measures and Performance on the CP Tests. One objective of the present study was to determine the relationship between neuropsychological

performance and the CP-dependent measures for the older adults. Scores from the full set of baseline neuropsychological assessments were combined into a set of five composite scores representing the conceptually motivated constructs [13, 65] of Memory Processing, Executive Functioning, Perceptual/Visual Processing, Conceptual Reasoning, and Organization/Attention using a method advocated by Cahn and colleagues [66] and Cohen and colleagues [67]. Each measure was converted into a z-score. The resulting z-scores for the measures within each construct were then averaged to derive a score for the constructed measure. The two Executive Function measures (Wisconsin Card Sorting Test: Trials to First Category, Total Number of Categories, and Failure to Maintain Set), which were not significantly correlated with the Executive Function composite variable, were removed from the composite, and the Executive Function composite was recomputed from the remaining measures in that set. Table 4 presents the group means on the pre- and postneuropsychological measures. Values under means are standard deviations; Table 5 displays the correlations between individual measures and their composite scores.

The correlation between the pretest scores of CP Test 1 and CP Test 2 was weak and nonsignificant ($r = .182$, $p = .087$) because the two dependent measures assessed different categorization constructs. The left columns of Table 6 contain the Pearson product-moment correlations between the composite scores and the categorization pretest measures (CP Test 1, CP Test 2, and Probe 1) for both groups of older adults. At Time 1 (pretest), CP Test 1 performance correlated significantly with all five composite indices; CP Test 2 correlated significantly with all indices except the Organization/Attention Composite. Probe 1 correlated with all the composite scores except the Perception/Visual Processing composite.

Finally, in order to examine whether neuropsychological measures could predict who benefited most from the categorization program, the z-score composite measures were correlated with the three difference scores (CP Test 1 posttest minus pretest, CP Test 2 posttest minus pretest, and Probe 3 minus Probe 1) using the data from the older adults who received the CP training. Additionally, partial correlations (using the pretest score as a covariate) between the composite scores and the categorization posttest measures (CP Test 1, CP Test 2, Probe 2, and Probe 3) were conducted. As can be seen in Table 6, the Perceptual/Visual, Conceptual/Reasoning, and Global Cognitive were the most useful composites in predicting improvement in performance on the CP-dependent measures.

4. Discussion

The current study is part of a systematic research program exploring the effects of a hierarchical cognitive training program in adult rehabilitation. The primary objective of the present study was to determine the utility of such training in healthy older adults and compare their performance to healthy young adults and to young adults with known neurocognitive deficits resulting from TBI. The results support the notion that older adults similar to adults with TBI can benefit from cognitive activities that enhance organization and conceptual knowledge. Overall, the three groups of participants who received the CP training demonstrated improvement in their categorization performance. Categorization in the project was measured directly by the two CP tests developed specifically for this training program. Participants who received the CP training showed improvement in their ability to categorize common objects as measured by their performance on CP Test 1. During CP Test 1, participants were required to describe objects effectively and to generate creative uses that could improve functional problem-solving abilities. Participants in the experimental groups demonstrated significant gains in describing common objects and in creative uses of objects. In comparison, participants in the control group did not demonstrate significant gains in this area. Greater gains however were noted in the young adults with TBI and young healthy adults, in comparison to the older experiment adult group.

CP Test 2 measures the ability to categorize based on predetermined rules. During this test, participants were provided the rule and asked to classify objects based on the rule. This type of task is considered passive in nature because participants were not required to delineate the rule themselves. In contrast, during the actual training tasks of the CP, participants were required to delineate the rule based on feedback they received from the clinician. While young participants (both with TBI and noninjured young adults) demonstrated significant improvement on the CP Test 2, older adults who received the training did not demonstrate significant gains. Therefore, it appears that older adults demonstrate greater gains in the classification of objects as compared to rule-based learning.

Older adults were followed up to four months upon completion of their training. This was not possible for the TBI group since completion of the CP training also coincided with discharge from the rehabilitation facility. Findings indicated that older adults who received the training were able to maintain their gains at one and four months posttraining. Future studies need to explore the posttraining effects systematically. This information can guide future research on the CP and on potential benefits of "tune-up" sessions at specified intervals.

One of the primary challenges faced by cognitive rehabilitation programs centers on the realization that knowledge acquired during training may not transfer into other novel (untrained) tasks. Transfer success may be influenced by a number of factors stemming from the nature of the tasks, types of stimuli, and cognitive distance between the trained task and the untrained task as well as unfamiliarity with the untrained task itself. This challenge in transferring skills from domain-specific to more general can limit the practical impact of cognitive training programs as well as the motivation of participants to continue their training. An additional variable that contributes to the aforementioned challenge might be the advanced age of some older participants (i.e., over 75), which in turn could create difficulties in learning, speed of information processing, mental flexibility, and reduction in strategy use [8].

Table 4: Performance on neuropsychological measures.

	Group 1: young adults with TBI (treated) $n = 15$		Group 2: young uninjured adults (treated) $n = 15$		Group 3: older adults (treated) $n = 14$		Group 4: older adults (untreated) $n = 14$	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
California Verbal Learning Test-R (CVLT-R)								
Total trials 1-5	51.0	55.5	58.93	65.80	47.14	49.64	45.43	49.50
	14.06	11.32	7.85	6.07	9.77	10.49	9.87	9.02
Short delay	8.27	11.1	12.33	14.80	8.92	10.54	9.57	11.00
	4.81	5.13	2.09	2.00	3.66	4.39	3.00	3.59
Long delay	9.27	11.6	14.93	13.60	10.92	9.00	11.14	9.50
	4.45	3.89	1.53	1.72	3.50	3.94	3.44	3.16
Rey Complex Figure (RCF)								
Copy	29.61	31.09	34.90	34.53	29.82	30.36	30.00	32.00
	7.38	4.67	1.56	2.36	6.47	6.72	6.10	3.68
Immediate	16.34	22.77	21.64	28.71	13.50	15.93	10.32	16.64
	6.83	5.47	4.57	5.39	8.20	8.27	5.03	5.92
Delayed	17.34	22.9	21.77	27.63	12.04	15.39	10.50	16.0
	6.33	5.26	4.74	6.44	5.96	8.81	5.88	5.72
Wechsler Memory Scale-III (WMS-III)								
Longest Digit Span Forward	7.5	8.6	6.53	6.93	6.78	6.57	6.57	6.36
	2.61	2.36	1.41	1.33	1.31	1.16	1.45	.84
Spatial Span Forward	8.28	9.54	8.93	9.27	7.79	8.00	7.50	7.78
	1.58	1.29	2.25	2.09	2.29	1.88	1.83	1.19
Spatial Span Backward	7.85	8.72	8.27	8.27	7.50	7.14	6.64	6.21
	1.65	1.67	2.02	1.79	1.45	1.83	1.39	1.05
Wisconsin Card Sorting Test (WCST)								
Number of Categories Completed	5.78	6.0	5.20	5.73	4.93	4.43	4.57	5.29
	.42	.0	1.57	.80	1.82	2.24	1.70	1.44
Trials to Complete First Category	13.21	11.36	14.67	13.27	17.43	12	16.28	16.28
	5.72	1.56	6.42	4.58	22.62	4.45	9.86	13.76
Failure to Maintain Set	.57	.27	.47	.27	1.14	1.14	.71	1.07
	.64	.46	.64	.59	1.29	2.03	1.07	1.64
Booklet Category Test								
Total errors	40.0	27.4	33.53	18.20	70.07	54.79	65.07	56.64
	20.58	14.02	25.90	17.04	21.54	24.15	28.96	31.04
Symbol Digits Modality Test	40.25	47.75	58.20	65.47	44.50	48.07	44.00	47.00
	10.11	10.71	9.51	13.17	15.00	11.59	9.37	11.71
Controlled Oral Word Association Test(COWAT)	33.1	41.7	42.73	49.47	39.29	39.78	41.93	41.86
	8.67	13.04	9.50	9.34	8.30	10.02	17.23	17.06
Trail Making Test A (in seconds)	36.16	38.98	25.67	23.10	34.61	35.36	39.93	36.86
	11.37	44.45	6.98	6.60	11.24	14.78	14.61	13.70
Trail Making Test B (in seconds)	79.5	90.54	57.45	55.80	79.43	74.57	74.21	86.57
	45.5	85.4	23.20	24.90	26.42	26.37	25.82	43.95
Woodcock-Johnson III (WJIII-13)								
Picture Recognition	48.42	51.42	53.33	54.53	51.86	50.43	51.21	51.86
	3.36	3.75	3.02	2.75	4.15	8.91	3.98	3.35
WJIII-3								
Spatial Relations	70.21	73.64	74.07	74.87	68.50	68.64	68.29	69.50
	5.1	5.41	6.28	5.45	6.34	9.64	7.18	6.46

Table 4: Continued.

	Group 1: young adults with TBI (treated) $n = 15$		Group 2: young uninjured adults (treated) $n = 15$		Group 3: older adults (treated) $n = 14$		Group 4: older adults (untreated) $n = 14$	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
WJIII-15								
Analysis/Synthesis	27.78	28.71	28.67	28.93	23.37	25.00	23.71	23.36
	2.42	2.16	4.35	4.68	6.06	5.72	4.07	7.24
WJIII-5								
Concept Formation	28.35	34.85	36.57	37.21	28.64	29.93	28.21	28.71
	5.3	4.18	2.93	5.29	7.80	6.76	6.04	7.50
WJIII-16								
Decision Speed	26.0	31.78	36.46	38.15	32.07	34.14	30.14	32.29
	8.35	7.29	5.59	3.29	5.81	6.02	6.19	6.13
WJIII-1								
Verbal Comprehension	52.92	56.14	59.57	61.50	56.43	56.78	58.28	57.93
	5.99	5.9	4.62	4.83	5.65	6.18	5.65	5.30

Hence, another important objective of the present study was to determine whether the CP training facilitates the ability to generalize categorization skills to novel tasks as measured by the probes. The current results indicated that our older adult group, similarly to adults with TBI, demonstrated gains in the probe performance. However, the gains of the young TBI group were greater than that of the older adult group. This might be due to the fact that the injured TBI group had a greater room for improvement on this task. Future studies may want to increase the complexity of the probe tasks in order to ensure that they provide opportunity for improvement in performance as a result of training.

4.1. Relationship between the CP Measures and Formal Neuropsychological Tests. Given the focus of CP Test 1 on object recognition and categorization, it is understandable that the skills this test measures overlap significantly with those assessed by the neuropsychological tests comprising the Perception Composite score and the Conceptual/Reasoning composite. On the other hand, rule-governed categorization has been consistently related to executive functioning, attention, and reasoning processes using a variety of methodologies [27, 29]. The present findings are largely consistent with this view as can be seen by the fact that composite measures having to do with executive function, attention, and reasoning correlate with performance on CP Test 2 during the pretest and posttest administrations. Probe task improvement is largely related to conceptual/reasoning and perceptual/visual measures, although this task may be affected by a ceiling effect. Finally, the Memory Composite and the Global Cognitive composite scores relate to all CP-dependent measures. The present findings with older adults are consistent with our previous work with the CP and TBI [13].

Future research should continue to explore the interaction between task properties and learner capacity. Evidence suggests [68] that individuals with high working memory capacities (as measured, for instance, by the digit span task) will learn rule-based problems faster than they can learn problems requiring a nonexplicit, similarity reasoning strategy. Alternatively, individuals with lower working memory capacity learn the nonrule-governed category structures faster than they learn those defined by rules. In the present study, baseline performance on the CP-dependent measures was highly correlated with the memory composite scores. This suggests that it may be profitable, in the designing of neurocognitive programs like the CP, to understand the relationship between individual neuropsychological characteristics and performance in categorization retraining tasks. The present study implemented composite scores in order to create theoretically meaningful constructs and also as a strategy to reduce the number of comparisons. Due to the preliminary nature of the findings and the small sample size, further corrections for multiple comparisons were not implemented. This limitation should be taken into consideration when interpreting the above findings.

4.2. Conclusions, Clinical Implications, Limitations, and Future Research. The present results contribute to the growing body of literature supporting cognitive training in healthy older adults. Improvements noted by cognitively healthy older adults and by younger participants with TBI, are consistent with our previous work implementing the CP with younger adults who sustained neuropsychological deficits secondary to closed head injury [12, 13]. However, gains demonstrated by older adults are not as dramatic as those demonstrated by their younger counterparts. Future research needs to determine the utility of the CP in treating older patients with TBI during rehabilitation and in the chronic phase post injury. This is in light of recent evidence on

Table 5: Pearson correlations between neuropsychological measures and constructed composite scores.

Measure	Composite
Memory Measures	Memory composite
CVLT Learning Curve: Trial 5-Trial 1	.487**
CVLT Total (Trial 1 through Trial 5)	.804**
CVLT Short Delay Free Recall	.853**
CVLT Short Delay Cued Recall	.882**
CVLT Long Delay Free Recall	.891**
CVLT Long Delay Cued Recall	.833**
Rey Figure Immediate Recall	.759**
Rey Figure Delayed Recall	.767**
Rey Figure Recognition	.415*
Digit Span Total Score	.353**
Spatial Span Total Score	.343*
Executive Function Measures	Executive composite
Symbol Digits Correct—Written	.798**
Trail Making Test A (seconds)	-.755**
Trail Making Test B (seconds)	-.832**
Booklet Category Test (total errors)	-.467*
Wisconsin Card Sort—Total # of Categories	.347
Wisconsin Card Sort—Trials to 1st Category	.012
Wisconsin Card Sort—Failure to Maintain Set	-.108
Wisconsin Card Sort—Learning to Learn (%)	.365*
COWAT total Score	.653**
Woodcock-Johnson Test 16—Decision Speed	.667**
Perception and Visual Processing Measures	Perception composite
Woodcock-Johnson Test 13 Picture Recognition	.881**
Woodcock-Johnson Test 3 Spatial Relations	.874**
Conceptual Processing and Reasoning Measures	Concept/ reasoning composite
Woodcock-Johnson Test 15 Analysis/Synthesis	.838**
Woodcock-Johnson Test 5 Concept Formation	.813**
Woodcock-Johnson Test 1 Verbal Comprehension	.747**
Organization and Attention Measures	
Rey Figure Score to Copy	-.720**
Rey Figure Time to Copy (seconds)	-.709**
General Cognitive Functioning	
WASI Verbal	.731**
WASI Performance	.831**
MMSE	.725**

Note: $^{*}p < .05$; $^{**}p < .01$.

the neurodegenerative effects of chronic TBI on the brain structure and function [35, 69].

The Task Force on Promotion and Dissemination of Psychological Procedures and the World Health Organization define efficacy research as the examination of an intervention's effect under highly controlled experimental conditions [50, 70]. The current results suggest that the CP training is efficacious in enhancing certain aspects of categorization performance. The CP training implemented a standardized, manualized protocol and followed the necessary procedures in order to adhere to the standards and rigor of experimental research. However, given the small sample sizes in the present study, the results should be interpreted with caution and could not be generalized to the larger population of TBI and older adults. Future research should incorporate larger sample sizes to reduplicate these findings and also incorporate quality of life outcome measures in order to determine the potential generalizability of cognitive training in other aspects of daily activities.

One of the strengths of the current project was the careful selection of participants in order to create a homogeneous sample of subjects, improve internal validity, and reduce variability in performance. In addition to determining the utility of the CP training in older adults with TBI, future research should include adults with mild cognitive decline in order to determine the potential utility of this type of training in adults who may be at risk for developing dementia.

Present findings with a small subgroup of older adults demonstrate that the positive effects of CP training last for up to 4 months post treatment. This finding can guide future research on determining the timing and potential benefit of periodic booster sessions. Additionally, the link between CP training and improving cognitive reserve in older adults may be a fruitful line of research. Furthermore, future studies exploring the long-term effects of treatment should incorporate older adults who do not receive the training in addition to both younger and older adults with TBI.

Biological aging does not seem to be a uniformed process; therefore, larger studies (with neurologically healthy and neurologically compromised groups of participants) will afford the necessary statistical power to identify subgroups of older adults and delineate who benefits the most from this type of training. The identification of individuals with specific neuropsychological and genetic (i.e., ApoE allele) profiles, determination of mitigating factors, and the development of predictive models indicating who would demonstrate the greatest gains would be an important contribution of larger scale studies.

In closing, the present results provide additional evidence supporting the continued investigation of the CP training in adult neurorehabilitation. Future larger scale clinical trials would provide stronger evidence for the CP utility. The long-term effects of CP training on categorization performance and the use of CP training in older participants who are at risk for dementia and in older adults with TBI would be a fruitful line of investigation.

Table 6: Pearson correlations between constructed composite scores and categorization measures (older adults only).

Measure	CP Test 1 (pre)	CP T2 (pre)	Probe 1	Probe 2^{+}	Probe 3^{+}	CP Test 1 (post)$^{+}$	CP Test 2 (post)$^{+}$	Post-pre CP Test 1	Post-pre CP T2	Probe 3-Probe 1
Memory composite	.609**	.530**	.407*	.697**	.089	.323	.277	.235	.273	.461
Executive Functioning composite	.398*	.446*	.365*	.342	.180	.244	.510	.047	.141	.458
Perception/Visual Processing composite	.673**	.422*	.227	.824**	.120	.740**	.503	.064	.468*	.310
Conceptual/Reasoning composite	.595**	.437**	.614**	.721**	.290	.541*	.449	.064	.401	.777**
Organization/Attention composite	.290	.177	.480**	.440	.424	.484	.463	.214	.174	.356
Global Cognitive composite	.609**	.517**	.343*	.864**	.096	.443	.537*	.004	.503*	.596*

Note: Executive Functioning composite does not include the following Wisconsin Card Sort Measures: Total Number of Categories, Trials to 1st Category, and Failure to Maintain Set. Posttests and pre-post difference scores include the experimental older participants only. $^{*}p < .05$; $^{**}p < .01$. + indicates partial correlations holding the corresponding pretest performance as a covariate.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request. Availability is dependent upon compliance with personal data protection laws and ethics board laws and regulations.

Conflicts of Interest

There are no conflicts of interest to report, financial or otherwise.

Acknowledgments

Special thanks are due to the study volunteers, to the clinical site collaborators at the Center for Neuro Skills (CNS), Bakersfield, CA; Center for Neuro Skills, Dallas, Texas; and Center for Comprehensive Services (CCS, NeuroRestorative), Carbondale, IL, and to the members of the NeuroCognitive Disorders Laboratory at Miami University for their contributions, especially Abigail Migut, Lacy Robinson, and Jessica Schneider. This research was supported in part by a grant from the Committee on Faculty Research at Miami University, Oxford, Ohio, where Constantinidou was Professor of Speech Pathology and Audiology. The statistical analyses, preparation, writing, and editing of this manuscript was supported by the author's current employer, the University of Cyprus, Nicosia, Cyprus.

References

[1] G. W. Rebok, K. Ball, L. T. Guey et al., "Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults," *Journal of the American Geriatrics Society*, vol. 62, no. 1, pp. 16–24, 2014.

[2] S.-C. Li, F. Schmiedek, O. Huxhold, C. Röcke, J. Smith, and U. Lindenberger, "Working memory plasticity in old age: Practice gain, transfer, and maintenance," *Psychology and Aging*, vol. 23, no. 4, pp. 731–742, 2008.

[3] E. Giogkaraki, M. P. Michaelides, and F. Constantinidou, "The role of cognitive reserve in cognitive aging: results from the neurocognitive study on aging," *Journal of Clinical and Experimental Neuropsychology*, vol. 35, no. 10, pp. 1024–1035, 2013.

[4] F. Constantinidou and S. Baker, "Stimulus modality and verbal learning performance in normal aging," *Brain and Language*, vol. 82, no. 3, pp. 296–311, 2002.

[5] A. W. Kaszniak, L. W. Poon, and W. H. Riege, "Assessing memory deficits: an information-processing approach," in *Handbook for Clinical Memory Assessment of Older Adults*, L. W. Poon, T. Crook, K. L. Davis, C. Eisdorfer, B. J. Gurland, A. W. Kaszniak, and L. W. Thompson, Eds., pp. 168–188, American Psychological Association, Washington D.C., 1986.

[6] F. Constantinidou and M. Ioannou, "The effects of age and language on paragraph recall performance: findings from a preliminary cross-sectional study," *Psychologia*, vol. 15, no. 4, pp. 342–361, 2008.

[7] F. Constantinidou, I. Zaganas, E. Papastefanakis, D. Kasselimis, A. Nidos, and P. G. Simos, "Age-related decline in verbal learning is moderated by demographic factors, working memory capacity, and presence of amnestic mild cognitive impairment," *Journal of the International Neuropsychological Society*, vol. 20, no. 8, pp. 822–835, 2014.

[8] P. L. Ackerman, R. Kanfer, and C. Calderwood, "Use it or lose it? Wii brain exercise practice and reading for domain knowledge," *Psychology and Aging*, vol. 25, no. 4, pp. 753–766, 2010.

[9] F. Constantinidou and R. D. Thomas, "Principles of cognitive rehabilitation in TBI: an integrative neuroscience approach," in *Traumatic Brain Injury: Rehabilitation, Treatment, and Case Management, Fourth Edition*, M. J. Ashley and D. A. Hovda, Eds., pp. 513–540, Taylor & Francis: CRC Press, 2017.

[10] J. Karbach and P. Verhaeghen, "Making working memory work: a meta-analysis of executive-control and working memory training in older adults," *Psychological Science*, vol. 25, no. 11, pp. 2027–2037, 2014.

[11] Y. Brehmer, H. Westerberg, and L. Bäckman, "Working-memory training in younger and older adults: training gains, transfer, and maintenance," *Frontiers in Human Neuroscience*, vol. 6, p. 63, 2012.

[12] F. Constantinidou, R. D. Thomas, V. L. Scharp, K. M. Laske, M. D. Hammerly, and S. Guitonde, "Effects of categorization training in patients with TBI during post-acute rehabilitation: preliminary findings," *The Journal of Head Trauma Rehabilitation*, vol. 20, no. 2, pp. 143–157, 2005.

[13] F. Constantinidou, R. D. Thomas, and L. Robinson, "Benefits of categorization training in patients with Traumatic Brain Injury during post–acute rehabilitation," *Journal of Head Trauma Rehabilitation*, vol. 23, no. 5, pp. 312–328, 2008.

[14] A. Caramazza and J. R. Shelton, "Domain-specific knowledge systems in the brain: the animate-inanimate distinction," *Journal of Cognitive Neuroscience*, vol. 10, no. 1, pp. 1–34, 1998.

[15] G. W. Humphreys, C. J. Price, and M. J. Riddoch, "From objects to names: a cognitive neuroscience approach," *Psychological Research*, vol. 62, no. 2-3, pp. 118–130, 1999.

[16] F. G. Ashby, L. A. Alfonso-Reese, A. U. Turken, and E. M. Waldron, "A neuropsychological theory of multiple systems in category learning," *Psychological Review*, vol. 105, no. 3, pp. 442–481, 1998.

[17] R. M. Nosofsky, "Exemplar-based approach to relating categorization, identification, ad recognition," in *Multidimensional Models of Perception and Cognition*, F. G. Ashby, Ed., pp. 363–393, Earlbaum, Hillsdale, NJ, 1992.

[18] M. A. Erickson, "Executive attention and task switching in category learning: evidence for stimulus-dependent representation," *Memory & Cognition*, vol. 36, no. 4, pp. 749–761, 2008.

[19] K. Patterson, P. J. Nestor, and T. T. Rogers, "Where do you know what you know? The representation of semantic knowledge in the human brain," *Nature Reviews Neuroscience*, vol. 8, no. 12, pp. 976–987, 2007.

[20] G. S. Cree and K. McRae, "Analyzing the factors underlying the structure and computation of the meaning of chipmunk, cherry, chisel, cheese, and cello (and many other such concrete nouns)," *Journal of Experimental Psychology: General*, vol. 132, no. 2, pp. 163–201, 2003.

[21] G. W. Humphreys and E. M. Forde, "Hierarchies, similarity, and interactivity in object recognition:"category-specific" neuropsychological deficits," *Behavioral and Brain Sciences*, vol. 24, no. 3, pp. 453–476, 2001.

[22] F. Constantinidou and A. Migut, "Common object categorization in TBI and in normal aging executive network functioning and implications for rehabilitation," *Journal of the*

International Neuropsychological Society, vol. 14, Supplement 1, p. 76, 2008.

[23] F. Constantinidou and L. T. Kreimer, "Feature description and categorization of common objects after traumatic brain injury: the effects of a multi-trial paradigm," *Brain and Language*, vol. 89, no. 1, pp. 216–225, 2004.

[24] F. G. Ashby and E. M. Waldron, "The neuropsychological bases of category learning," *Current Directions in Psychological Science*, vol. 9, no. 1, pp. 10–14, 2000.

[25] F. Constantinidou and R. D. Thomas, "Principles of cognitive rehabilitation in TBI: an integrative neuroscience approach," in *Traumatic Brain Injury: Rehabilitation, Treatment, and Case Management*, M. Ashley, Ed., pp. 549–582, Taylor & Francis: CRC Press, 2010.

[26] F. G. Ashby, S. Noble, J. V. Filoteo, E. M. Waldron, and S. W. Ell, "Category learning deficits in Parkinson's disease," *Neuropsychology*, vol. 17, no. 1, pp. 115–124, 2003.

[27] F. G. Ashby and B. J. Spiering, "The neurobiology of category learning," *Behavioral and Cognitive Neuroscience Reviews*, vol. 3, no. 2, pp. 101–113, 2004.

[28] W. T. Maddox, B. C. Love, B. D. Glass, and J. V. Filoteo, "When more is less: feedback effects in perceptual category learning," *Cognition*, vol. 108, no. 2, pp. 578–589, 2008.

[29] W. T. Maddox and F. G. Ashby, "Dissociating explicit and procedural-learning based systems of perceptual category learning," *Behavioural Processes*, vol. 66, no. 3, pp. 309–332, 2004.

[30] W. T. Maddox and J. V. Filoteo, "Striatal contributions to category learning: quantitative modeling of simple linear and complex nonlinear rule learning in patients with Parkinson's disease," *Journal of the International Neuropsychological Society*, vol. 7, no. 6, pp. 710–727, 2001.

[31] A. M. Brickman, K. L. Siedlecki, J. Muraskin et al., "White matter hyperintensities and cognition: testing the reserve hypothesis," *Neurobiology of Aging*, vol. 32, no. 9, pp. 1588–1598, 2011.

[32] J. J. Breunig, M. V. Guillot-Sestier, and T. Town, "Brain injury, neuroinflammation and Alzheimer's disease," *Frontiers in Aging Neuroscience*, vol. 5, p. 26, 2013.

[33] J. J. Iliff, M. J. Chen, B. A. Plog et al., "Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury," *Journal of Neuroscience*, vol. 34, no. 49, pp. 16180–16193, 2014.

[34] V. E. Johnson, W. Stewart, and D. H. Smith, "Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans," *Brain Pathology*, vol. 22, no. 2, pp. 142–149, 2012.

[35] N. Konstantinou, E. Pettemeridou, I. Seimenis et al., "Assessing the relationship between neurocognitive performance and brain volume in chronic moderate-severe traumatic brain injury," *Frontiers in Neurology*, vol. 7, p. 29, 2016.

[36] E. Pettemeridou and F. Constantinidou, "Brain reserve as a predictor of functional outcome in chronic moderate-to-severe TBI," *Archives of Physical Medicine and Rehabilitation*, vol. 99, no. 10, article e39, 2018.

[37] M. L. Daviglus, C. C. Bell, W. Berrettini et al., "National Institutes of Health state-of-the-science conference statement: preventing Alzheimer disease and cognitive decline," *Annals of Internal Medicine*, vol. 153, no. 3, pp. 176–181, 2010.

[38] F. Constantinidou, R. D. Thomas, and P. Best, "Principles of cognitive rehabilitation after traumatic brain injury: a systematic hierarchical approach," in *Traumatic Brain Injury Rehabilitation*, M. Ashley and F. T. Constantinidou, Eds., pp. 337–365, CRC Publishers, Boca Raton, FL, 2nd edition, 2004.

[39] F. Constantinidou, "The categorization program," in *This is a copyright protected therapy program and manual designed to treat adults with cognitive-communication disorders*, Miami University. United States Library of Congress, copyright office (TXU 001345058), Oxford, OH, 2006.

[40] M. Gentilini, P. Nichelli, and R. Schoenhuber, "Assessment of attention in mild head injury," in *Mild Head Injury*, H. S. Levin, H. M. Eisenberg, and A. L. Benton, Eds., pp. 163–175, Oxford University Press, New York, 1989.

[41] T. Kay, D. E. Harrington, R. Adams et al., "Definition of mild traumatic brain injury," *Journal of Head Trauma Rehabilitation*, vol. 8, no. 3, pp. 86-87, 1993.

[42] C. Hagen, D. Malkmus, and P. Durham, "Levels of cognitive functioning," in *Rehabilitation of the Head-Injured Adult: Comprehensive Physical Management*, C. A. Downey, Ed., Professional Staff Association of Rancho Los Amigos Hospital, 1972.

[43] H. S. Levin, M. A. O'Donnell, and R. G. Grossman, *Galveston Orientation and Amnesia Test (GOAT): A Practical Scale to Assess Cognition after Head Injury*, Williams & Wilkins, Baltimore, 1979.

[44] American Psychiatric Association, *DSM-IV: The Diagnostic and Statistical Manual of Mental Disorders*, The Psychological Corporation, San Antonio, 1994.

[45] A. T. Beck, R. A. Steer, and G. K. Brown, *The Beck Depression Inventory-II*, The Psychological Corporation, San Antonio, 1996.

[46] H. Goodglass, E. Kaplan, and B. Barresi, *Boston Diagnostic Aphasia Examination*, The Psychological Corporation, San Antonio, TX, 3rd edition, 2000.

[47] F. Dutton, "Ishihara test for color blindness," 1999, March 2000, http://www.toledo-bend.com/colorblind/Ishihara.html.

[48] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state": a practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[49] B. B. Adamovich, J. A. Henderson, and S. Auerbach, *Cognitive Rehabilitation of Closed Head Injured Patients: A Dynamic Approach*, College Hill Press, San Diego, Ca, 1985.

[50] C. A. Coelho, F. DeRuyter, and M. Stein, "Treatment efficacy: cognitive-communicative disorders resulting from traumatic brain injury in adults," *Journal of Speech and Hearing Research*, vol. 39, no. 5, pp. S5–S17, 1996.

[51] M. D. Lezak, *Neuropsychological Assessment*, Oxford University Press, New York, 3rd edition, 1995.

[52] A. R. Luria, *Restoration of Function after Brain Injury*, Pergamon Press, Oxford, 1963.

[53] S. M. Zeno, S. H. Ivens, R. T. Millard, and R. Duvvuri, *The Educator's Word Frequency Guide*, Touchstone Applied Science Associates, New York, 1995.

[54] D. Wechsler, *Wechsler Abbreviated Scale of Intelligence*, The Psychological Corporation, San Antonio, 1999.

[55] M. F. Folstein, S. E. Folstein, and P. R. McHugh, *Mini Mental State Examination*, Psychological Assessment Resources, Inc., Lutz, FL, 2001.

[56] J. E. Myers and K. R. Meyers, *Rey Complex Figure Test and Recognition Trial*, Psychological Assessment Resources, Inc., Odessa, FL, 1995.

[57] M. D. Lezak, *Neuropsychological Assessment*, Oxford University Press, New York, 2nd edition, 1983.

[58] D. Wechsler, *Wechsler Memory Scale*, The Psychological Corporation, San Antonio, TX, 3rd edition, 1999.

[59] D. C. Delis, J. H. Kramer, E. Kaplan, and B. A. Ober, *California Verbal Learning Test*, The Psychological Corporation, San Antonio, TX, 2nd edition, 2000.

[60] D. A. Grant and E. A. Berg, *Wisconsin Card Sorting Test*, Los Angeles, Western Psychological Services, 1981.

[61] N. A. De Filippis and E. McCambell, *Booklet Category Test*, Psychological Assessment Resources, Inc., Odessa, FL, 2nd edition, 1998.

[62] A. Smith, *Symbol Digit Modalities Test*, Western Psychological Services, Los Angeles, 1973.

[63] A. Benton and K. Hamsher, *Multilingual Aphasia Examination*, University of Iowa Press, Iowa City, 1978.

[64] R. W. Woodcock, K. S. McGrew, and N. Mather, *Woodcock Johnson Tests of Cognitive Abilities*, Riverside Publishing, Itasca, IL, 3rd edition, 2001.

[65] M. D. Lezak, D. B. Howieson, and D. W. Loring, *Neuropsychological Assessment*, Oxford University Press, Oxford, 4th edition, 2004.

[66] D. A. Cahn, E. V. Sullivan, P. K. Shear, A. Pfefferbaum, G. Heit, and G. Silverberg, "Differential contributions of cognitive and motor component processes to physical and instrumental activities of daily living in Parkinson's disease," *Archives of Clinical Neuropsychology*, vol. 13, no. 7, pp. 575–583, 1998.

[67] J. Cohen, P. Cohen, S. G. West, and L. S. Aiken, *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*, Erlbaum, Hillsdale, NJ, 3rd edition, 2003.

[68] M. S. DeCaro, R. D. Thomas, and S. L. Beilock, "Individual differences in category learning: sometimes less working memory capacity is better than more," *Cognition*, vol. 107, no. 1, pp. 284–294, 2008.

[69] N. Konstantinou, E. Pettemeridou, E. A. Stamatakis, I. Seimenis, and F. Constantinidou, "Altered resting functional connectivity is related to cognitive outcome in males with moderate-severe Traumatic Brain Injury," *Frontiers in Neurology*, vol. 9, article 1163, 2019.

[70] Task Force on Promotion and Dissemination of Psychological Procedures, "Training in and dissemination of empirically validated psychological treatments," *The Clinical Psychologist*, vol. 48, pp. 13–23, 1995.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 9894571, 10 pages
https://doi.org/10.1155/2019/9894571

Review Article

From Broca and Wernicke to the Neuromodulation Era: Insights of Brain Language Networks for Neurorehabilitation

Grigorios Nasios,[1] **Efthymios Dardiotis**,[2] **and Lambros Messinis**[3]

[1]*Department of Speech and Language Therapy, University of Ioannina, Ioannina, Greece*
[2]*Department of Neurology, University Hospital of Larisa, University of Thessaly, Larisa, Greece*
[3]*Neuropsychology Section, Departments of Neurology and Psychiatry, University of Patras Medical School, Patras, Greece*

Correspondence should be addressed to Grigorios Nasios; grigoriosnasios@gmail.com

Received 27 January 2019; Revised 18 June 2019; Accepted 5 July 2019; Published 22 July 2019

Academic Editor: Antonio Pisani

Copyright © 2019 Grigorios Nasios et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Communication in humans activates almost every part of the brain. Of course, the use of language predominates, but other cognitive functions such as attention, memory, emotion, and executive processes are also involved. However, in order to explain how our brain "understands," "speaks," and "writes," and in order to rehabilitate aphasic disorders, neuroscience has faced the challenge for years to reveal the responsible neural networks. Broca and Wernicke (and Lichtheim and many others), during the 19th century, when brain research was mainly observational and autopsy driven, offered fundamental knowledge about the brain and language, so the Wernicke-Geschwind model appeared and aphasiology during the 20th century was based on it. This model is still useful for a first approach into the classical categorization of aphasic syndromes, but it is outdated, because it does not adequately describe the neural networks relevant for language, and it offers a modular perspective, focusing mainly on cortical structures. During the last three decades, neuroscience conquered new imaging, recording, and manipulation techniques for brain research, and a new model of the functional neuroanatomy of language was developed, the dual stream model, consisting of two interacting networks ("streams"), one ventral, bilaterally organized, for language comprehension, and one dorsal, left hemisphere dominant, for production. This new model also has its limitations but helps us to understand, among others, why patients with different brain lesions can have similar language impairments. Furthermore, interesting aspects arise from studying language functions in aging brains (and also in young, developing brains) and in cognitively impaired patients and neuromodulation effects on reorganization of brain networks subserving language. In this selective review, we discuss methods for coupling new knowledge regarding the functional reorganization of the brain with sophisticated techniques capable of activating the available supportive networks in order to provide improved neurorehabilitation strategies for people suffering from neurogenic communication disorders.

1. Introduction

Let us consider two healthy men, without a history of neurological disease, one 20 and one 80 years old, who both participated in a sentence comprehension task and showed the same success at comprehending sentences. The older individual is able (under circumstances) to perform similarly with the younger one, due to the compensatory recruitment of novel, ancillary brain regions [1]. These ancillary regions although available are not necessary in the younger person's brain. This phenomenon, which cannot be observed clinically but can be captured by functional resonance imaging, is "hidden" presbyphasia and in simple words tells us that an aged brain requires more effort to perform similarly to the younger one. The above simple paradigm offers a new perspective for the neuroanatomy of language and can be observed under various points of view: the brain's multifunctionality, its structural and functional connectivity, plasticity, and cognitive reserve hypothesis. It helps us to see the whole brain as an organ of communication, where linguistic and cognitive networks uninterruptedly cooperate. In our recently published editorial, we highlight, based on evidence

from healthy and diseased brains, its ability to make communication possible through meaningful symbols, expressions, and comprehension of ideas and concepts [2]. This selective review begins with a brief description of the Broca-Wernicke-Lichtheim-Geschwind classical model, from the era of autopsy-driven research. Then, Hickok and Poeppel's dual stream model of language processing is described, including its limitations (i.e., the role of the cerebellum). It then continues with a discussion of the ability to use language to communicate, which relies not only on the traditionally described core language networks but also on other additional, widely distributed, networks, which can be recruited to support linguistic functions when needed. New insights are offered by studying language in the aging brain and also language in young/developing brains. We also comment on the linkage between language and cognition especially in the elderly, as well as in poststroke aphasia, and the reorganization of language networks. Describing these networks, testing for their availability, and enhancing their recruitment constitute the science of neurorehabilitation. The newly conquered tools for clinical and experimental applications of neuroimaging and neuromodulation, i.e., artificial manipulation of brain activity, assisted neuroscience to establish a new era. By utilizing these modern methods, we have advanced our knowledge and subsequently challenged the classical knowledge about the brain and language. In the final part of this paper, we discuss methods for coupling the obtained new knowledge with sophisticated techniques in order to advance neurorehabilitation. We intentionally highlight numerous aspects of brain and language associations that could give rise to ideas on new therapeutic targets for people living with aphasia.

2. The Broca-Wernicke-Lichtheim-Geschwind Classical Model

Broca (1824-1880) first described in 1861, after autopsying the brain of his famous patient "Tan" (Louis Victor Leborgne), the association between motor aphasia and a lesion in the middle part of the patient's left frontal lobe, the cortical speech center, an area later named after him, as "Broca's area" [3, 4]. Shortly after Broca published his findings, Wernicke (1848-1905) noticed that not all language deficits were the result of damage to Broca's area. He observed in 1873 that damage to the left posterior superior temporal gyrus, now referred to as Wernicke's area, resulted in deficits in language comprehension, an aphasia later known as Wernicke's aphasia (receptive aphasia) [5]. Ludwig Lichtheim (1845-1928) described thoroughly the elements of conduction aphasia and developed an explanation of language processing in the brain. Furthermore, he developed an early model about the neuroanatomy of language, the so-called Wernicke-Lichtheim model. Later, during the 20th century, Norman Geschwind (1926-1984), a pioneering American behavioral neurologist, revived the Wernicke-Lichtheim model for the neuroanatomy of language so that the model is more widely known as the "Wernicke-Geschwind" model. According to this model, the sounds of the words are transferred through the auditory pathways to the primary auditory cortex and then to Wernicke's area, where the meaning of the words is extracted. In order for a person to produce speech, the meanings of words are sent from Wernicke's area via the arcuate fasciculus to Broca's area, where morphemes are formed and then passed on to the motor cortex. On the other hand, information from the written word is transferred through the primary visual cortex to the angular gyrus and then to Wernicke's area. To do justice, we should refer to the model that predominated for more than a century as the standard neurological model of language, the Broca-Wernicke-Lichtheim-Geschwind model.

In this historical model, Wernicke's and Broca's areas are connected to each other by the arcuate fasciculus. Where exactly Broca's and Wernicke's areas are located in the brain is also a matter of ambiguity, especially for the latter. Broca's area corresponds to the triangular and opercular inferior frontal gyrus (IFG) of the left hemisphere for the majority of humans. Dronkers and colleagues, reinspecting with high-resolution magnetic resonance imaging the preserved brains of Broca's two historic patients, found that both patients' lesions extended significantly not only to the surface lesions, originally observed by Broca, but also into medial regions of the brain [6]. Furthermore, Fedorenko and colleagues presented evidence from single-subject fMRI studies suggesting that Broca's area contains two sets of subregions, one specific for language, surrounded by another, nonlanguage-specific, engaged in a wide range of cognitive tasks [7]. One could argue this in favor of the brain's multifunctionality.

As for Wernicke's area, the ambiguity is even higher, with Mesulam and colleagues arguing that there is no single area in our brain dedicated to speech comprehension [8]. Studying a large group of primary progressive aphasia patients, they found a heterogeneous set of cortical atrophy sites associated with severe comprehension impairments for sentence production, including Wernicke's area, Broca's area, and the dorsal premotor cortex, while severe comprehension impairments for single words were associated with atrophy sites in the left temporal pole and adjacent anterior temporal cortex.

The simplified modular approach of the classical model is perhaps still useful for understanding the classical categorization of aphasic syndromes, in which frontal lesions cause motor aphasias, temporal and temporal-parietal lesions cause sensory aphasias, lesions affecting the arcuate fasciculus cause conduction aphasia, and deeper cortical lesions cause disconnection syndromes. This model which dominates in many classical (and not necessarily old) textbooks, and guided research until the beginning of this century, is now outdated. It proved that "it is linguistically and anatomically underspecified" [9] and could not scientifically support the full range of aphasic syndromes. Trembley and Dick [10] reviewed the serious gaps of the classical model and commented that one of the most important problems was "the lack of circuit information regarding the neural connections of the brain areas involved." One other major concern is that this model focuses on cortical structures, excluding subcortical regions and relevant connections, based on an outdated

Table 1: Dual stream model: main hubs and white matter connections of the dorsal and ventral pathways for language processing.

	Dorsal stream (left dominant)	Ventral stream (bilaterally distributed)
Main "hubs"	(i) Inferior frontal gyrus (ii) Ventral portions of the precentral gyrus (iii) Anterior portions of the insula (iv) Posterior sector of the insula (v) Ventral portions of the supramarginal gyrus (vi) Area Spt	(i) Superior temporal gyrus (STG) (ii) Superior temporal sulcus (STS) (iii) Middle and inferior temporal gyri (MTG/ITG)—anterior temporal lobe (ATL)
Main fascicles	(i) Articulate fasciculus (AF) (ii) Posterior components of the superior longitudinal fascicle (SLF)	(i) External capsule (EC) (ii) Inferior fronto-occipital fascicle (IFOF) (iii) Inferior longitudinal fascicle (ILF) (iv) Uncinate fascicle (UF)

brain anatomy. During the last three decades, studies based mainly on functional neuroimaging provided proof that during comprehension, both temporal lobes were involved, and during speech production, a wide range of frontal and parietal regions, usually in the left hemisphere, are activated. Furthermore, many subcortical regions and tracts are involved. Interestingly, Behroozmand et al. provide novel evidence that the subthalamic nucleus is involved in vocal motor function as demonstrated after deep brain stimulation treatment of patients with PD [11], forming together the core language networks.

3. Hickok and Poeppel's Dual Stream Model and the Language Processing Networks

A fundamental shift away from the older models to modern network-based models was made possible through new knowledge from observations on both human and nonhuman primates [12]. Modern network-based models are composed of parallel and interconnected streams, involving both cortical and subcortical areas. Hickok and Poeppel [13, 14] proposed the "dual stream" model, emphasizing speech processing in "dorsal" and "ventral" pathways (streams): the ventral stream is largely bilaterally organized from the temporal pole to the basal occipitotemporal cortex, processing speech signals for comprehension, while the dorsal stream is strongly left hemisphere dominant, from the posterior superior temporal to the inferior frontal cortices [15]. The function of the dorsal stream is mainly restricted to the "sensory-motor mapping of sound to articulation" [16].

According to the dual stream model, the dorsal pathway involves left hemispheric structures in the posterior frontal lobe, the posterior dorsal temporal lobe, and the parietal operculum, including long white matter (WM) tracts connecting the frontal to the temporal and parietal lobes, namely, the articulate fasciculus (AF), and the indirect anterior and indirect posterior components of the superior longitudinal fascicle (SLF). More specifically, the core anterior (frontal) hubs of the dorsal pathway include the inferior frontal gyrus (opercular and triangular part), the ventral portions of the precentral gyrus, and the anterior portions of the insula (forming together the left frontal operculum (L-FO)). Posteriorly, the main hubs are the posterior sector of the insula, the ventral portions of the supramarginal gyrus, and Sylvian parietal temporal region (Spt), forming, together with the upper parts of the posterior superior temporal gyrus and sulcus, the left temporoparietal junction (L-TPJ).

Area Spt is located in the posterior part of the left planum temporale (PT) region, where speech perception and production systems converge. Despite its proximity to classical Wernicke's area, its posterior part is mainly involved in speech production, acting as a "computational hub" and a sensorimotor interface between the two streams.

On the other hand, ventral pathways are bilaterally distributed into both hemispheres, and the major hubs include the superior temporal gyrus (STG), superior temporal sulcus (STS), middle and inferior temporal gyri (MTG/ITG), and the anterior temporal lobe (ATL). The ventral stream connects the frontal cortices to the occipital, parietal, and temporal lobes, via long white matter (WM) tracts, including the external capsule (EC), the inferior fronto-occipital fascicle (IFOF), the inferior longitudinal fascicle (ILF), and the uncinate fascicle (UF). The main hubs and fascicles constituting the dual stream model are summarized in Table 1.

Although the dual stream model describes the anatomical foundations of normal, and not disordered, speech and language processing, studies from stroke patients with aphasia offered evidence supporting it. Kümmerer et al. assessed, in a large sample of 100 aphasic stroke patients, how well acute impairments of repetition and comprehension correlate with lesions of either the dorsal or ventral stream [17]. They concluded that task performance on auditory comprehension measures requires an interaction between temporal and prefrontal brain regions via the ventral extreme capsule pathway. Fridriksson et al. also examined the effect of both cortical damage and disconnection on aphasic impairment in stroke patients, in the context of this model [18]. They found that "measures of motor speech impairment are more strongly associated with damage to the dorsal stream, whereas measures of impaired speech comprehension with ventral stream involvement." Interestingly and importantly, they showed that language functions such as naming, speech repetition, and grammatical processing rely on a broader network and on interactions between the two streams. Their results offer evidence from brain-damaged patients supporting the dual model, by linking motor speech impairment mostly

with damage to the dorsal stream and impaired speech comprehension with ventral stream involvement. Furthermore, they showed that elements such as naming, speech repetition, and grammatical processing rely mainly on connections and interactions between the two streams. This explains why patients with seemingly disparate lesion locations often experience similar impairments on specific speech or language tasks: they may have dissimilar cortical damage, but this damage affects the same broad cortical network that supports these tasks. Overall, these findings help us to move from a nodular to a network perspective. Of course, there are key regions, in other words, crucial central nodes or hubs, many of them described by the 19th century aphasiologists, but the way they connect and interact with other nodes and tracts provides our brain with its unique capacity for language processing and communication. In addition to these hubs, language networks also include important "bottleneck" areas, referred to below.

A novel synthesis of old and new knowledge about the architecture of the language processing network, in alignment with the dual stream model, is provided by the work of Mirman et al. [19]. In this inspired study, the researchers combined high-quality structural neuroimaging analysis techniques and extensive behavioral assessment of 99 patients with persistent acquired language deficits, in order to answer questions about the functional and neural organization of language processing in patients with acquired language deficits. Two major divisions within the language system can be identified: one serving "meaning versus form" and one for "recognition versus production." The peri-Sylvian regions involved in phonological processing were either supra-Sylvian (for speech production—in agreement with the dorsal stream) or infra-Sylvian (for speech recognition—in agreement with the ventral stream). On the other hand, semantic production and recognition deficits were linked with damage in extra-Sylvian regions. More specifically, semantic production deficits, reflected in semantic errors, were linked to the left anterior temporal lobe (ATL), while semantic multimodal recognition deficits (were linked) to impaired white matter connectivity of other brain regions with the frontal cortex, respectively. Mirman et al. with their work highlighted the importance of mainly three tracts beyond the arcuate fasciculus: the uncinate fasciculus, the inferior fronto-occipital fasciculus, and the anterior thalamic radiations. All these fiber tracts converge in a "bottleneck" frontal white matter region, where even nonsevere damage can impair semantic processing across multiple tasks and modalities. Outside this bottleneck region, more extensive lesions would be required to produce comparable multimodal semantic deficits. This is why lesions in other regions known to be important for semantic processing, such as the middle and posterior portions of the middle temporal gyrus and the inferior parietal lobule, were not associated in this study with either semantic errors or multimodal semantics. The role of these regions is neither specific to semantically driven word production (that role is played by the left ATL) nor general enough for focal damage to produce multimodal semantic deficits, as is the white matter bottleneck region.

4. The Role of the Cerebellum

As we noted previously, the cerebellum does not appear either in the classical or in the modern models describing the neuroanatomy of language. This is not what really happens, however. Cerebellar lesions are reported to cause aphasia [20], and the cerebellum's role in a wide range of nervous system cognitive and affective functions, among them language, has been revealed [21]. A topologic distinction has been established between the "motor" cerebellum, projecting to the cortical motor areas, and the "cognitive/affective" cerebellum, connected with the cortical and limbic association areas [22]. Cerebellar lesions have a remote functional impact on structurally intact cortical regions via crossed cerebello-cerebral diaschisis. Mariën and Borgatti [22] discuss about (strongly lateralized) involvement of the cerebellum in a broad spectrum of nonmotor language functions through a dense network of crossed and reciprocal cerebello-cerebral connections. Recently, the cerebellum was targeted with tDCS (transcranial direct current stimulation) with enhancing effects on verbal fluency [23]. It is time therefore to include the cerebellum in a new, updated, "multiple stream model" of language processing.

5. Beyond Networking: Communication and Our Brain

Many neuroscientists, from neuroanatomists to neurolinguists, focus their research on specific small particles of language processing. These efforts together contributed deep inside our brains as communication organs and form our current knowledge on language functions and cognitive-linguistic interactions both in health and disease. An example on this is the findings from one of our recent studies, in which we examined verb-noun dissociations in patients with relapsing remitting multiple sclerosis and reported for the first time in the literature a noun superiority over verbs for picture confrontation naming in these patients [24]. However, in the real world, our brain seems to organize its interactions for communication under scenarios involving multifunctional processing of multimodal input from the environment. In simple words, what we are prepared to listen to is preformed depending on whether we are discussing with friends or attending a scientific lecture. Different groups of words, forming different groups of meanings, connected with different emotional aspects, involve different parts of our brain, far beyond the strictly defined language networks. Huth and colleagues shifted our thinking to this real world using a novel generative model to create a detailed semantic atlas [25]. They wanted to answer questions about the extension and the selectivity of brain regions involved in the representation of the meaning of language. With voxel-wise modeling of functional MRI (fMRI) data, they found that words related to the same semantic domain were highly correlated, while nonrelated words were not. Doing this for several hundreds of words, using a large corpus of English text of narrative stories, subjects were listening to for hours, while in the scanner, they showed that most areas within the semantic system represent information about specific

semantic domains. In this way, they were able to form an atlas showing which domains are represented in each area. Additionally, they proved that the semantic system was highly consistent across the participating individuals, and they explained this consistency due to their common life experiences. One other major finding of this genius study was that the distribution of semantically selective areas within the semantic system was relatively symmetrical across the two cerebral hemispheres. This latter finding is inconsistent with human lesion studies that support the idea that semantic representation is lateralized to the left hemisphere but, however, in alignment with the bilateral distribution of the ventral stream of the dual stream model. The bilateral distribution of semantic representation, in other words the extension of the ventral stream into both hemispheres, is strongly supported by numerous studies, since neuroimaging technology allowed us to study language in healthy individuals, as Price excellently reviewed [26, 27].

When we communicate, words predominate in our message exchange network, but we never only exchange words. Different brain areas scan prosody, emotions, body language, and various environmental stimuli. There are no simple rules about the hierarchy of what is more important for our brain in order to "understand" a message. Evidence to help us unravel this hierarchy can be obtained by studying brain-lesioned patients, and this could guide neurorehabilitation. We admire the way Sacks, before the functional imaging and brain networking era, described in the 9th chapter ("The President's Speech") of his book *The Man Who Mistook His Wife for a Hat* that only the people who were unable to understand words were able to really understand the speaker [28]. We (GN) are now preparing a case report of a 67-year-old man who after an excellent recovery from his aphasia due to a left hemispheric (mainly temporal) stroke ten years ago reappeared a few months ago with severe aphasia, after a right temporal stroke. Could this be interpreted as a case of "aphasia due to right hemispheric lesion" in a patient with a proven "left dominant brain"? Are we justified to answer "no"? Turkeltaub et al. reported a similar very interesting case of a 72-year-old aphasic woman who experienced beneficial effects in naming after being treated with an inhibitory TMS protocol targeting her right pars triangularis, until a new, right hemispheric stroke caused worsening of her aphasia [29]. These cases bring in mind the historical Barlow 1877 case [30], while Hamilton and colleagues review similar other reported cases trying to illuminate the right hemisphere's role in poststroke aphasia recovery [31]. How can these paradoxical observations be explained? Why, even though we know that right hemisphere homologue areas are active during language tasks, do lesions in these areas not typically (but exceptionally) cause language impairment? It may not be the inhibited or lesioned right hemispheric areas per se that matter more but their role within the language networks. When the core left hemispheric language areas are intact, many right homologue ones remain "silent," but in left hemispheric-lesioned brains, their role appears to be protagonistic. If also these right hemispheric areas are destroyed (as in Turkeltaub et al.'s patient—and an ischemic lesion could not be equivalent to a TMS-induced inhibition), aphasia worsens.

As Cahana-Amitay and Albert point out in their excellent book *Redefining Recovery from Aphasia*, a multifunctional neural model of language should be formed, including brain language mappings that reflect the functional diversity of the neural networks subserving language and the role of nonlinguistic skills [32]. Of course, by establishing the brain areas which are responsible for various task conditions, we do not reach the end of the road. Neuroscience's goal still remains to explain how the brain does it [33].

6. Language and the Aging Brain

Investigating possible effects of aging on the brain's structural and functional characteristics is not only important for better understanding neuroplasticity changes of language networks but also due to the fact that the majority of patients with aphasia (due to stroke or neurodegenerative diseases) are elderly. However, current knowledge on brain language maps is typically based on neural data collected from young healthy adults (usually college-aged students), whose functional neuroanatomy is likely distinct from that of older adults in important ways [32].

It has been argued that even though normal aging impairs specific aspects of language production, most core language processes are robust to brain aging [34]. However, as it has recently been reported, young people outperform their older counterparts during semantic tasks [35]. Older adults display less activation than young people in some elements of the typical left hemisphere semantic network but greater activation in right frontal and parietal regions, principally when they perform more poorly than the younger participants. Thus, semantic processing in later life is associated with a shift from semantic-specific to other neural resources.

Agarwal et al. compared two groups of younger and older adults with equivalent cognitive performance, during a word retrieval task, with a multifaceted approach, integrating structural and functional imaging data, on interactions between hemispheres or reorganization of dominant hemisphere networks, resulting in preservation of function [36]. The authors demonstrated that left hemispheric language areas showed higher functional connectivity in older adults with intact behavioral performance and, thus, may have a role in preserving function. Successful language ability among older adults depends on sparing of cognitive abilities, where "the combined contribution of preserved cognitive functions reflects a compensatory mechanism recruited to support a given compromised linguistic function" [32]. Whether this reorganization and overactivation of various, ancillary networks always represent a "successful" compensation, or not, is of course a question that remains unanswered [37]. One could speculate that cognitive decline, especially as far as executive functions are concerned, could be the most relevant explanation of language decline in the elderly and perhaps vice versa. Language keeps the brain active in many aspects, for example, bilingual older adults typically have

better performance on tasks of executive control than do monolingual peers. Grady et al. studied brain network activity in monolingual and bilingual older adults and found that bilinguals showed stronger correlations than monolinguals between intrinsic connectivity in the frontoparietal control network and task-related increases of activity in prefrontal and parietal regions [38]. The authors conclude that bilingual differences in network connectivity suggest that language experience begun in childhood and continued throughout adulthood which influences brain networks in ways that may provide benefits in later life. These benefits protect or enhance the brain's executive control systems and may delay the onset of Alzheimer's disease symptoms [39]. This provides further support for multifunctional, mutually interacting perspectives, whereby a constant and dynamic interaction exists among neural networks subserving cognitive, affective, and praxic functions on the one hand and linguistic functions on the other. Of course, further studies, not only in the elderly but also through the entire lifespan, are needed to track the changes that occur in the brain mechanisms underlying cognitive and linguistic processes [37].

7. A Note for Young/Developing Brains and Reorganization of Language Networks

Research not only on the aging but also on the developing brains offers insights on various aspects on brain reorganization of language functions. One aspect is the evolution and improvement of linguistic proficiency during the first years of life. Lidzba et al. [40] studied language representation and lateralization in 36 children, adolescents, and young adults, using a language comprehension and a language production task during fMRI. They found that the neural basis of language comprehension is established in a bilateral network by late childhood, while for the productive network, an increase with age both in focus and lateralization was seen. Furthermore, in 24% of their sample, language comprehension and language production were lateralized to opposite hemispheres. Another very interesting aspect was the way that congenital left hemispheric brain lesions were compensated for, as language is concerned. This question is of special interest since previous work has shown that children with congenital left hemisphere damage scored far better in language production tasks than left hemisphere-damaged adults [41]. Another interesting point is that perinatal stroke patients exhibit different patterns of reorganization than childhood stroke patients. Childhood stroke patients showed left-side cortical activation, similar to controls, while perinatal stroke patients showed atypical right-side or bilateral language lateralization [42]. What Lidzba et al. found in their study [40] which corresponds to the dual stream model is that language comprehension is represented more bilaterally than language production. Moreover, a hemispheric dissociation with left hemispheric language production but bilateral or right hemispheric language comprehension is not uncommon even in healthy right-handed subjects.

The Tübingen group addressed the question of how congenital left hemispheric brain lesions affecting language were compensated for [43]. They tried to link lesion characteristics and interhemispheric reorganization, depending on the level of reorganized language production, and comprehension. They observed that patients with lesions in areas belonging to the dorsal stream of the language network such as the insular cortex and the temporoparietal junction (TPJ) showed reorganization of both language production and comprehension more frequently. In other words, the integrity of the dorsal stream might be crucial for a normal left-lateralized language development. The finding that damage to the structures of the dorsal network and not the ventral may lead to reorganization of the networks that support language may be explained by the unilateral dominance (usually left side) of the dorsal network as compared to the bilateral organization of the ventral network. As a consequence, a congenital lesion of the dorsal language pathway in the left hemisphere may induce interhemispheric reorganization of the entire language network, including language comprehension [43]. As regards the TPJ area, although structurally it is placed between the dorsal and ventral networks and despite its proximity to the classical Wernicke's area, its posterior part is mainly involved in speech production. For a detailed description of this area, refer to the book by Hickok and Small [44].

8. The Role of Neurorehabilitation for Recovery from Aphasia

Aphasias, the acquired language disorders occurring after disruption of language networks, are a common consequence of stroke and other brain disorders and traditionally are treated by speech and language therapy. The classical speech and language therapy approaches are purely linguistic and vary mainly in the intervention methodology, its duration, intensity, and frequency [45]. These approaches however do not do justice to patients recovering from aphasia. First of all, left hemispheric stroke patients with aphasia may also have cognitive deficits, especially on working memory and sustained attention, and there is an established association between them and aphasia severity [46]. Further evidence for the relationship between linguistic and cognitive functions in patients with poststroke aphasia is provided by Yu et al. [47]. This group assessed these functions in 63 poststroke patients with aphasia using the second edition of the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) battery and the Western Aphasia Battery (WAB). Data obtained by multiple regression analyses showed a close relationship between linguistic and multiple cognitive functions [47].

As it has been stated, there are important "nonlinguistic factors that participate in reshaping the neural networks supporting recovery of language functions in aphasia" in the concept of neural multifunctionality [32]. Medications for auxiliary use in the treatment of aphasia have shown mixed and rather moderate success, with most notable language improvement found with memantine, vasopressin, and piracetam and only when combined with behavioral speech treatment [48]. Hillis et al. [49] recently showed that stroke aphasic patients with damage in the left posterior superior temporal gyrus (pSTG) and/or superior longitudinal

fasciculus/arcuate fasciculus (SLF/AF) and showed better naming outcome when administered Selective Serotonin Reuptake Inhibitors (SSRIs) for 3 months after their stroke. This suggests that the outcome might be modulated by SSRIs. There are two more reports on the possible positive effect of SSRIs on stroke patients, one showing better outcome in cognitive functions with escitalopram [50] and another in motor functions with fluoxetine; the result in both studies was independent of depression [51]. Whether this could implicate that SSRIs may modulate brain plasticity after stroke is an ongoing and exciting question. Approaching poststroke aphasia in terms of disrupted networks coupled with understanding how mechanisms of ischemic brain injury may be influenced by therapeutic interventions can offer better treatment strategies of poststroke aphasia in the future [52].

We now know that recovery from aphasia relies upon supportive, ancillary networks, serving as a reserve capacity. The brain must therefore be functionally reorganized, and when brain regions involved in recovery remain intact, the outcome is more favorable and vice versa. Neuroplasticity is the driving force for this functional reorganization, and neurorehabilitation is the science of enhancing it. Saur et al. studied patients with aphasia after stroke, by utilizing repeated functional MRI (fMRI) with parallel language testing [53]. They wanted to unravel the dynamics of reorganization in the language system from the acute to the chronic stage. Their findings indicated that brain reorganization during language recovery proceeds in three phases. Firstly, in the acute phase, there is a strongly reduced activation of the remaining left language areas. Secondly, an upregulation takes place with recruitment of homologue language zones, associated with improvement, and thirdly, there is a normalization of activation. A possible explanation of this normalization of activation reflects a consolidation in the language system.

An important question arising from studies like the previous one is whether the pattern of network reorganization for residual language function and recovery is consistent across aphasic patients. Turkeltaub et al. addressed this question performing a meta-analysis of functional neuroimaging studies of chronic aphasia after stroke, and they answered it positively [54]. Three distinct areas were recruited during recovery: spared left hemispheric areas belonging to a language network, new left hemispheric areas, and homotopic (to the left language areas) right hemispheric ones. The recruitment of new areas can either act compensatory or may hinder recovery. The authors conclude that the consistency in network recruitment can help us to form better rehabilitation protocols by targeting these networks. What we have learned so far from the neurorehabilitation of language functions is that aphasic patients need a holistic cognitive neurorehabilitation approach, designed and conducted by a multidisciplinary team, with neuroimaging and neuromodulation playing a protagonistic role [55].

9. Language and Neuromodulation

Transcranial magnetic stimulation (TMS) is a neurostimulatory and neuromodulatory technique, based on the principle of electromagnetic induction of an electric field in the brain. It has behavioral consequences and therapeutic potentials, capable of evoking long-lasting cumulative plastic changes in the stimulated cortex and also in the remote functionally interconnected areas, enhancing the brain's functional capacity and showing beneficial effects on cognitive performance in healthy persons and in patients with various neurological diseases [56]. For aphasia recovery, rTMS (repetitive TMS) has been used to inhibit activation of functional networks contralateral to the lesion (in the unaffected hemisphere, transcallosal inhibition) that actually hinders recovery. This effect can be visualized by neuroimaging [57]. Targeting these areas (and more specifically the triangular part of the right inferior frontal gyrus (IFG)) with low-frequency, inhibitory rTMS has a positive effect on language recovery in patients with aphasia following stroke [58, 59]. An important point for rTMS application is the need to stimulate the same cortical area, and this can be achieved by using brain MRI data of the treated individual to calculate the correct positioning of the coil with new generation rTMS devices by utilizing neuronavigation techniques.

Another promising neurostimulation technique is transcranial direct current stimulation (tDCS), which has already been used for improving language functions during the last decade [60]. Martin et al. investigated the behavioral and neural effects of tDCS during simultaneous fMRI in healthy young and older participants, performing semantic fluency and motor speech tasks [61]. During the stimulation conditions, performance in these tasks significantly and comparably improved in both age groups. They identified tDCS effects in the ventral and dorsal anterior cingulate regions, with an additional effect of enhanced left network laterality on older adults. Fiori et al. investigated how tDCS modulates connectivity in the language networks of healthy individuals [62]. They combined a verb learning paradigm during functional neuroimaging with simultaneous anodal tDCS over the left inferior frontal gyrus (IFG) in healthy human volunteers. They found that stimulation with anodal tDCS significantly resulted in improved performance and also caused alteration (decrease) of task-related functional connectivity between the left IFG and the right insula. This demonstrated that the behavioral improvements induced by anodal tDCS were related to an altered connectivity within a large language network. It might appear paradox, of how implementation of anodal tDCS, which has known excitatory effects, results in improved performance and also in decreased activity over the targeted left IFG. Nevertheless, this phenomenon has also been described in other studies. Holland et al. [63], in one of the few studies in the literature combining tDCS with neuroimaging techniques, investigated in healthy subjects the effect of anodal tDCS over the left IFC during concurrent fMRI in picture naming. They found that, relative to sham, it significantly facilitated the response, while on the neural level, it significantly decreased task-related activity in the stimulated inferior frontal regions. In another study, Meinzer et al. [64] targeted the left IFC in healthy elderly adults using fMRI and concurrent anodal tDCS, to assess immediate effects on cognition, with a group of younger adults serving as

controls. The stimulation significantly improved performance in older adults and significantly reduced task-related hyperactivity in bilateral prefrontal cortices, inducing a more "youth-like" connectivity pattern during RS-fMRI. The authors suggest that tDCS not only modulated endogenous low-frequency oscillations in the targeted brain area but also spread to functionally connected areas of the language network. The observed reduced activity over the left frontal regions in all the above-mentioned studies can be explained as a tDCS-induced neuronal adaptation over these areas resulting in behavioral improvement. This adaptation is probably a regulation of overactivity of the targeted areas, representing a "priming" effect in neuronal level [63, 65].

Evidence is now emerging that significant improvement can be achieved in patients with poststroke aphasia combining tDCS neuromodulation and behavioral interventions [66–68]. Compared to rTMS, tDCS has certain practical advantages. tDCS devices are portable and affordable and could be easily applicable even on a home basis, making them widely available for neurorehabilitation and telerehabilitation interventions. tDCS can be applied on either the left (anodal-excitatory) or the right (cathodal-inhibitory) hemispheres, but it can also be prompted for bilateral concurrent stimulation [69]. Of course, its effectiveness and safety for various conditions must first be established, and permissions from regulatory authorities must be obtained. Furthermore, a consensus on where favorable brain changes occur to support aphasia recovery does not yet exist [68].

10. Conclusions

In the past, language representation in the brain was considered as being modular, and under this concept, speech treatment was limited to linguistic tasks and conducted separately for each module (i.e., naming or syntax). We now know that language functions stream widely throughout our brain and are interconnected with many other brain functions. We also recognize the brain's multifunctionality and the mechanisms for its functional reorganization. This new knowledge, coupled with technological progress, with new sophisticated and widely available and affordable tools for neuroimaging and neuromodulation, as well as telerehabilitation, will shift clinical neuroscience to an era of improved therapeutic strategies for people living with language and communication disorders.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

All authors contributed to the conception, drafting, revising, and finalizing of the manuscript and agreed to be accountable for all aspects of the work.

References

[1] A. Wingfield and M. Grossman, "Language and the aging brain: patterns of neural compensation revealed by functional brain imaging," *Journal of Neurophysiology*, vol. 96, no. 6, pp. 2830–2839, 2006.

[2] G. Nasios and L. Messinis, "Neuroanatomy of language: new insights from lesioned and healthy brains," *EC Neurology*, vol. 10, no. 5, pp. 343–345, 2018.

[3] P. P. Broca, "Perte de la Parole, Ramollissement Chronique et Destruction Partielle du Lobe Antérieur Gauche du Cerveau," *Bulletin de la Société Anthropologique*, vol. 2, pp. 235–238, 1861.

[4] N. Mohammed, V. Narayan, D. P. Patra, and A. Nanda, "Historical vignette, Louis Victor Leborgne ("Tan")," *World Neurosurgery*, vol. 114, pp. 121–125, 2018.

[5] K. Wernicke, *Der aphasische Symptomencomplex: Eine psychologische Studie auf anatomischer Basis*, Ed. Max Cohn&Weigert, Breslau, 1874.

[6] N. F. Dronkers, O. Plaisant, M. T. Iba-Zizen, and E. A. Cabanis, "Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong," *Brain*, vol. 130, no. 5, pp. 1432–1441, 2007.

[7] E. Fedorenko, J. Duncan, and N. Kanwisher, "Language-selective and domain-general regions lie side by side within Broca's area," *Current Biology*, vol. 22, no. 21, pp. 2059–2062, 2012.

[8] M. M. Mesulam, C. K. Thompson, S. Weintraub, and E. J. Rogalski, "The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia," *Brain*, vol. 138, no. 8, pp. 2423–2437, 2015.

[9] D. Poeppel and G. Hickok, "Towards a new functional anatomy of language," *Cognition*, vol. 92, no. 1-2, pp. 1–12, 2004.

[10] P. Trembley and A. S. Dick, "Broca and Wernicke are dead, or moving past the classic model of language neurobiology," *Brain and Language*, vol. 162, pp. 60–71, 2016.

[11] R. Behroozmand, K. Johari, R. M. Kelley, E. C. Kapnoula, N. S. Narayanan, and J. D. W. Greenlee, "Effect of deep brain stimulation on vocal motor control mechanisms in Parkinson's disease," *Parkinsonism & Related Disorders*, 2019.

[12] E. F. Chang, K. P. Raygor, and M. S. Berger, "Contemporary model of language organization: an overview for neurosurgeons," *Journal of Neurosurgery*, vol. 122, no. 2, pp. 250–261, 2015.

[13] G. Hickok and D. Poeppel, "Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language," *Cognition*, vol. 92, no. 1-2, pp. 67–99, 2004.

[14] G. Hickok and D. Poeppel, "The cortical organization of speech processing," *Nature Reviews Neuroscience*, vol. 8, no. 5, pp. 393–402, 2007.

[15] G. Hickok and D. Poeppel, "Neural basis of speech perception," *Handbook of Clinical Neurology*, vol. 129, pp. 149–160, 2015.

[16] D. Saur, B. W. Kreher, S. Schnell et al., "Ventral and dorsal pathways for language," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 46, pp. 18035–18040, 2008.

[17] D. Kümmerer, G. Hartwigsen, P. Kellmeyer et al., "Damage to ventral and dorsal language pathways in acute aphasia," *Brain*, vol. 136, no. 2, pp. 619–629, 2013.

[18] J. Fridriksson, D. B. den Ouden, A. E. Hillis et al., "Anatomy of aphasia revisited," *Brain*, vol. 141, no. 3, pp. 848–862, 2018.

[19] D. Mirman, Q. Chen, Y. Zhang et al., "Neural organization of spoken language revealed by lesion–symptom mapping," *Nature Communications*, vol. 6, no. 1, p. 6762, 2015.

[20] H. J. De Smet, P. Paquier, J. Verhoeven, and P. Mariën, "The cerebellum: its role in language and related cognitive and affective functions," *Brain and Language*, vol. 127, no. 3, pp. 334–342, 2013.

[21] X. Guell, J. D. E. Gabrieli, and J. D. Schmahmann, "Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort," *NeuroImage*, vol. 172, pp. 437–449, 2018.

[22] P. Mariën and R. Borgatti, "Language and the cerebellum," *Handbook of Clinical Neurology*, vol. 154, pp. 181–202, 2018.

[23] P. E. Turkeltaub, M. K. Swears, A. M. D'Mello, and C. J. Stoodley, "Cerebellar tDCS as a novel treatment for aphasia? Evidence from behavioral and resting-state functional connectivity data in healthy adults," *Restorative Neurology and Neuroscience*, vol. 34, no. 4, pp. 491–505, 2016.

[24] M. Kambanaros, L. Messinis, G. Nasios, A. Nousia, and P. Papathanasopoulos, "Verb–noun dissociations in relapsing-remitting multiple sclerosis: verb effects of semantic complexity and phonological relatedness," *Aphasiology*, vol. 31, no. 1, pp. 49–66, 2017.

[25] A. G. Huth, W. A. De Heer, T. L. Griffiths, F. E. Theunissen, and J. L. Gallant, "Natural speech reveals the semantic maps that tile human cerebral cortex," *Nature*, vol. 532, no. 7600, pp. 453–458, 2016.

[26] C. J. Price, "A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading," *Neuroimage*, vol. 62, no. 2, pp. 816–847, 2012.

[27] C. J. Price, "The anatomy of language: a review of 100 fMRI studies published in 2009," *Annals of the New York Academy of Sciences*, vol. 1191, no. 1, pp. 62–88, 2010.

[28] O. Sacks, "The man who mistook his wife for a hat and other clinical tales," in Harper & Row, New York, USA, 1985.

[29] P. E. Turkeltaub, H. B. Coslett, A. L. Thomas et al., "The right hemisphere is not unitary in its role in aphasia recovery," *Cortex*, vol. 48, no. 9, pp. 1179–1186, 2012.

[30] T. Barlow, "On a case of double hemiplegia, with cerebral symmetrical lesions," *British Medical Journal*, vol. 2, no. 865, pp. 103-104, 1877.

[31] R. H. Hamilton, E. G. Chrysikou, and B. Coslett, "Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation," *Brain Lang*, vol. 118, no. 1-2, pp. 40–50, 2011.

[32] D. Cahana-Amitay and M. Albert, *Redefining recovery from aphasia*, Oxford University Press, New York, NY, USA, 2015.

[33] L. W. Barsalou, "What does semantic tiling of the cortex tell us about semantics?," *Neuropsychologia*, vol. 105, pp. 18–38, 2017.

[34] M. A. Shafto and L. K. Tyler, "Language in the aging brain: the network dynamics of cognitive decline and preservation," *Science*, vol. 346, no. 6209, pp. 583–587, 2014.

[35] P. Hoffman and A. M. Morcom, "Age-related changes in the neural networks supporting semantic cognition: a meta-analysis of 47 functional neuroimaging studies," *Neuroscience and Biobehavioral Reviews*, vol. 84, pp. 134–150, 2018.

[36] S. Agarwal, E. A. Stamatakis, S. Geva, and E. A. Warburton, "Dominant hemisphere functional networks compensate for structural connectivity loss to preserve phonological retrieval with aging," *Brain and Behavior*, vol. 6, no. 9, article e00495, 2016.

[37] C. Grady, "The cognitive neuroscience of ageing," *Nature Reviews Neuroscience*, vol. 13, no. 7, pp. 491–505, 2012.

[38] C. L. Grady, G. Luk, F. I. M. Craik, and E. Bialystok, "Brain network activity in monolingual and bilingual older adults," *Neuropsychologia*, vol. 66, pp. 170–181, 2015.

[39] B. T. Gold, "Lifelong bilingualism and neural reserve against Alzheimer's disease: a review of findings and potential mechanisms," *Behavioural Brain Research*, vol. 281, pp. 9–15, 2015.

[40] K. Lidzba, E. Schwilling, W. Grodd, I. Krägeloh-Mann, and M. Wilke, "Language comprehension vs. language production: age effects on fMRI activation," *Brain and Language*, vol. 119, no. 1, pp. 6–15, 2011.

[41] E. Bates, J. Reilly, B. Wulfeck et al., "Differential effects of unilateral lesions on language production in children and adults," *Brain and Language*, vol. 79, no. 2, pp. 223–265, 2001.

[42] P. Ilves, T. Tomberg, J. Kepler et al., "Different plasticity patterns of language function in children with perinatal and childhood stroke," *Journal of Child Neurology*, vol. 29, no. 6, pp. 756–764, 2014.

[43] K. Lidzba, B. de Haan, M. Wilke, I. Krägeloh-Mann, and M. Staudt, "Lesion characteristics driving right-hemispheric language reorganization in congenital left-hemispheric brain damage," *Brain and Language*, vol. 173, pp. 1–9, 2017.

[44] G. Hickok and S. L. Small, *Neurobiology of Language*, Elsevier, 2016.

[45] M. C. Brady, H. Kelly, J. Godwin, and P. Enderby, "Speech and language therapy for aphasia following stroke," *Cochrane Database of Systematic Reviews*, vol. 5, article CD000425, 2012.

[46] B. Lee and S. B. Pyun, "Characteristics of cognitive impairment in patients with post-stroke aphasia," *Annals of Rehabilitation Medicine*, vol. 38, no. 6, pp. 759–765, 2014.

[47] Z. Z. Yu, S. J. Jiang, S. Bi, J. Li, D. Lei, and L. L. Sun, "Relationship between linguistic functions and cognitive functions in a clinical study of Chinese patients with post-stroke aphasia," *Chinese Medical Journal*, vol. 126, no. 7, pp. 1252–1256, 2013.

[48] D. Cahana-Amitay, M. L. Albert, and A. Oveis, "Psycholinguistics of aphasia pharmacotherapy: asking the right questions," *Aphasiology*, vol. 28, no. 2, pp. 133–154, 2013.

[49] A. E. Hillis, Y. Y. Beh, R. Sebastian et al., "Predicting recovery in acute poststroke aphasia," *Annals of Neurology*, vol. 83, no. 3, pp. 612–622, 2018.

[50] R. E. Jorge, L. Acion, D. Moser, H. P. Adams, and R. G. Robinson, "Escitalopram and enhancement of cognitive recovery following stroke," *Archives of General Psychiatry*, vol. 67, no. 2, pp. 187–196, 2010.

[51] F. Chollet, J. Tardy, J.-F. Albucher et al., "Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial," *The Lancet Neurology*, vol. 10, no. 2, pp. 123–130, 2011.

[52] A. Thiel and A. Zumbansen, "The pathophysiology of post-stroke aphasia: a network approach," *Restorative Neurology and Neuroscience*, vol. 34, no. 4, pp. 507–518, 2016.

[53] D. Saur, R. Lange, A. Baumgaertner et al., "Dynamics of language reorganization after stroke," *Brain*, vol. 129, no. 6, pp. 1371–1384, 2006.

[54] P. E. Turkeltaub, S. Messing, C. Norise, and R. H. Hamilton, "Are networks for residual language function and recovery

consistent across aphasic patients?," *Neurology*, vol. 76, no. 20, pp. 1726–1734, 2011.

[55] G. Nasios and L. Messinis, "Brain functional reorganization after stroke: what has recovery from aphasia taught us?," *EC Neurology*, vol. 10, no. 7, pp. 584–586, 2018.

[56] G. Nasios, L. Messinis, E. Dardiotis, and P. Papathanasopoulos, "Repetitive transcranial magnetic stimulation, cognition, and multiple sclerosis: an overview," *Behavioural Neurology*, vol. 2018, Article ID 8584653, 8 pages, 2018.

[57] W. D. Heiss, "Imaging effects related to language improvements by rTMS," *Restorative Neurology and Neuroscience*, vol. 34, no. 4, pp. 531–536, 2016.

[58] C. L. Ren, G. F. Zhang, N. Xia et al., "Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials," *PLoS One*, vol. 9, no. 7, article e102557, 2014.

[59] M. Haghighi, M. Mazdeh, N. Ranjbar, and M. A. Seifrabie, "Further evidence of the positive influence of repetitive transcranial magnetic stimulation on speech and language in patients with aphasia after stroke: results from a double-blind intervention with sham condition," *Neuropsychobiology*, vol. 75, no. 4, pp. 185–192, 2017.

[60] S. Wortman-Jutt and D. J. Edwards, "Transcranial direct current stimulation in poststroke aphasia recovery," *Stroke*, vol. 48, no. 3, pp. 820–826, 2017.

[61] A. K. Martin, M. Meinzer, R. Lindenberg, M. M. Sieg, L. Nachtigall, and A. Flöel, "Effects of transcranial direct current stimulation on neural networks in young and older adults," *Journal of Cognitive Neuroscience*, vol. 29, no. 11, pp. 1817–1828, 2017.

[62] V. Fiori, L. Kunz, P. Kuhnke, P. Marangolo, and G. Hartwigsen, "Transcranial direct current stimulation (tDCS) facilitates verb learning by altering effective connectivity in the healthy brain," *NeuroImage*, vol. 181, pp. 550–559, 2018.

[63] R. Holland, A. P. Leff, O. Josephs et al., "Speech facilitation by left inferior frontal cortex stimulation," *Current Biology*, vol. 21, no. 16, pp. 1403–1407, 2011.

[64] M. Meinzer, R. Lindenberg, D. Antonenko, T. Flaisch, and A. Flöel, "Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes," *The Journal of Neuroscience*, vol. 33, no. 30, pp. 12470–12478, 2013.

[65] G. Hartwigsen, "Adaptive plasticity in the healthy language network: implications for language recovery after stroke," *Neural Plasticity*, vol. 2016, Article ID 9674790, 18 pages, 2016.

[66] P. P. Shah-Basak, R. Wurzman, J. B. Purcell, F. Gervits, and R. Hamilton, "Fields or flows? A comparative meta-analysis of transcranial magnetic and direct current stimulation to treat post-stroke aphasia," *Restorative Neurology and Neuroscience*, vol. 34, no. 4, pp. 537–558, 2016.

[67] P. Marangolo, "The potential effects of transcranial direct current stimulation (tDCS) on language functioning: combining neuromodulation and behavioral intervention in aphasia," *Neuroscience Letters*, 2017.

[68] R. Sebastian, K. Tsapkini, and D. C. Tippett, "Transcranial direct current stimulation in post stroke aphasia and primary progressive aphasia: current knowledge and future clinical applications," *NeuroRehabilitation*, vol. 39, no. 1, pp. 141–152, 2016.

[69] M. Sandars, L. Cloutman, and A. M. Woollams, "Taking sides: an integrative review of the impact of laterality and polarity on efficacy of therapeutic transcranial direct current stimulation for anomia in chronic poststroke aphasia," *Neural Plasticity*, vol. 2016, Article ID 8428256, 21 pages, 2016.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 1803624, 13 pages
https://doi.org/10.1155/2019/1803624

Review Article

Addressing Evidence Linking Secondary Alexithymia to Aberrant Humor Processing

Panayiotis Patrikelis,[1,2] Giuliana Lucci,[2] Athanasia Alexoudi,[1] Stefanos Korfias,[1] Lambros Messinis,[3] Grigorios Nasios,[4] Themistoklis Papasilekas,[1] Damianos Sakas,[1] and Stylianos Gatzonis[1]

[1]*First Department of Neurosurgery, Medical School, National and Kapodistrian University of Athens, Greece*
[2]*Department of Technologies, Communication and Society, International University of Rome "G. Marconi", Italy*
[3]*Neuropsychology Section, Departments of Neurology and Psychiatry, University Hospital of Patras and University of Patras Medical School, Greece*
[4]*Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina, Greece*

Correspondence should be addressed to Panayiotis Patrikelis; ppatrik@cc.uoi.gr

Received 26 January 2019; Revised 9 May 2019; Accepted 14 May 2019; Published 18 July 2019

Academic Editor: Norbert Kovács

Copyright © 2019 Panayiotis Patrikelis et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In this review, we explore current literature and assess evidence linking secondary (acquired) alexithymia to aberrant humor processing, in terms of their neurobiological underpinnings. In addition, we suggest a possible common neuropathological substrate between secondary alexithymia and deficits in humor appreciation, by drawing on neurophysiologic and neuroradiological evidence, as well as on a recent and unique single-case study showing the cooccurrence of secondary alexithymia and deficit in humor appreciation. In summary, what emerges from the literature is that the cortical midline structures, in particular the medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC), and the insular cortex, seem to play a crucial role in the expression of both alexithymia and defective humor processing, while though to a lesser extent, a right hemisphere and bilateral frontoparietal contribution becomes evident. Neurobiological evidence of secondary alexithymia and aberrant humor processing points to the putative role of ACC/mPFC and the insular cortex in representing crucial processing nodes whose damage may produce both the above clinical conditions. We believe that the association of secondary alexithymia and aberrant humor processing, especially humor appreciation deficit, and their correlation with specific brain regions, mainly ACG/mPFC, as emerged from the literature, may be of some heuristic importance. Increased awareness on this topic may be of aid for neurosurgeons when accessing emotion-relevant structures, as well as for neuropsychologists to intensify their efforts to plan evidence-based neurorehabilitative interventions to alleviate the deleterious effects of such interpersonal communication deficits.

1. Introduction

Alexithymia, literally meaning "without words for emotions", is used in the nosologic nomenclature to describe (1) a specific disturbance of emotional processing such as difficulties in identifying and verbalizing emotions, (2) difficulty in distinguishing between feelings and somatic sensations that accompany emotional arousal, and (3) externally oriented thinking and impaired symbolic activity [1, 2].

The prevalence of alexithymia is fairly high among patients with psychiatric disorders [3], since alexithymia may predispose to or even exacerbate preexisting psychopathology. It has been seen that alexithymic individuals may often show significantly higher levels of "functional" somatic and psychiatric symptoms such as anxiety and depression than nonalexithymics (e.g., [4]). For instance, among patients with conversion disorder, alexithymia was higher among those who attempted suicide [5]. Literature views a

possible relationship between alexithymia and increased suicide risk as mediated by depressive symptoms (for a review see [6]). Moreover, in a prototypical study assessing the relationships between alexithymia, suicidal ideation, and serum lipid levels in a sample of drug-naïve adult outpatients with obsessive compulsive disorder (OCD), it has been seen that alexithymics with comorbid OCD may exhibit deregulation of the cholesterol balance, which in turn may be linked to suicidal ideation [7].

Alexithymia observed in people who have suffered from brain injury and manifesting symptoms resembling those of primary (congenital) alexithymia is referred to as "acquired alexithymia" or "secondary alexithymia." Clinical cases of secondary alexithymia are largely neglected and not well understood [8]. What we know is that secondary alexithymia is often more resistant to treatment [9] and is not associated with a specific premorbid personality, while on the other hand it presents with cognitive impairment [10].

The lack of the sense of humor is another important aspect of alexithymia that should be further investigated, especially since the ability to produce and comprehend humor is a critical interpersonal ability in promoting suitable social interactions. Humorlessness, besides other subjective symptoms, i.e., lack of insight, emotional distance, somatizing tendency, and rigidity, are often reported by alexithymic individuals and their relatives [11], though they are not part of the core symptoms of alexithymia.

In this review, we attempt to explore current literature and evaluate evidence linking secondary alexithymia to aberrant humor processing, in terms of their neurobiological underpinnings. In addition, we suggest a possible common neuropathological substrate between secondary alexithymia and deficits in humor appreciation, by drawing on neurophysiological and neuroradiological evidence, as well as on a recent and unique single-case study showing the cooccurrence of secondary alexithymia and deficit in humor appreciation [12]. However, our main objective is to launch theoretical reflections about a putative neurobiological rapport relating secondary alexithymia and aberrant humor processing, particularly in the direction of a selective anterior cortical midline structure involvement as suggested by our prototypic case study [12], and supported to some extend by the relevant literature on secondary alexithymia, with the latter providing evidence of an also right hemisphere involvement. On the contrary, it is beyond the scope of this paper to provide a complete and detailed account of the literature and relative data. Therefore, our report focuses on the most relevant/interesting studies relating to this goal instead of considering a complete literature panorama.

2. Secondary Alexithymia Theories

The most relevant theories regarding the aetiology of secondary alexithymia emphasize the role of neurophysiological factors. The most prominent among them, proposed by Hoppe and Bogen [13], links alexithymia to a functional commissurotomy, which is an interhemispheric inhibition resembling the state of surgical cerebral commissurotomy sectioning the corpus callosum [14]. The authors [7] suggest that abnormal interhemispheric communication reduces coordination and integration of specialized functions, determining an abnormal state of inhibition of neural information, normally transmitted from one hemisphere to another throughout the corpus callosum.

Lane et al. [15] proposed an Anterior Cingulate Cortex (ACC) damage hypothesis linking alexithymia to ACC activity deficit during states of emotional arousal. They reported a strong correlation between emotional arousal and blood flow in the cingulate cortex of a female sample whose emotional awareness was assessed before PET imaging.

Some authors have associated alexithymic features with right hemisphere damage following stroke [16] consistently with the role of the right hemisphere in emotion processing [17, 18]. According to this alexithymia's right hemisphere activation hypothesis, the genesis of alexithymia implies a relation between the activation levels of the right hemisphere and alexithymia features, i.e., alexithymic patients could suffer a deficit in the right hemisphere emotional processing [8, 19].

By contrast, Becerra et al. [20] reported the case of a patient who developed alexithymia following a motor vehicle accident that is inconsistent with both functional commissurotomy and the ACC damage hypothesis, given that the damage of their patient was confined to the lateral, rather than medial, aspects of the cortex, in particular in the lateral frontal and parietal lobes. Moreover, the patient's damage was not confined to the right hemisphere, but rather distributed between both hemispheres, weakening the alexithymia's right hemisphere activation hypothesis.

Furthermore, a defective emotional verbal labeling hypothesis has been advanced [21], suggesting a defective emotional information transfer from the right hemisphere to the "language centre" of the left hemisphere that makes impossible labeling emotional information. Others have suggested that once the orderly linkage from body stimuli to emotions and symbolic language fails to work, a poor symbolization of bodily information and alexithymia is induced [22]. More specifically, such linkage is assumed to be mediated by the default mode network, i.e., a set of functionally interconnected brain nodes including the dorsal and ventral medial prefrontal cortex, the medial and lateral parietal cortex, the posterior cingulate cortex, and the temporal cortex [23–25].

Hobson et al. [26] suggested that impaired object-naming ability is linked to alexithymia, particularly whenever emotional identification is called upon. They also supported a large body of evidence for a putative link between verbal abilities and alexithymia, regarding both secondary alexithymia and developmental cases. Evidence of impaired interoceptive functioning in alexithymic persons supports the key role of general interoceptive impairment in giving rise to alexithymia [27, 28]. In brief, damage to areas in the inferior frontal gyrus, commonly considered to be an important language region, and in the anterior insula support the notion that alexithymia may arise from disruption in both language and interoception.

Schäfer et al. [29] reported the case of a patient who sustained a right anterior cingulate infarct. Specifically, MRI

revealed a large recent infarct in the right ACC and in the adjacent corpus callosum. The lesion spread into the middle portion of the medial frontal cortex, while there was a small infarct lesion in the posterior part of the corpus callosum. The patient manifested an alexithymia-like disorder, as well as abnormal emotion processing including a right hemisphere emotional face perception deficit, as confirmed by ERP recordings.

The authors [29] hypothesized that such a lesion produced a sort of pathological interference in a critical node of a large-scale network subserving affective control of behavior. Ho and Lee [30] presented the case of a woman who, after falling to the ground during horse riding and crushing her skull, became alexithymic as a result of damage in her right primary visual cortex (Brodmann Area 18/19), suggesting that emotional dysfunctions, although frequently associated with abnormal "top-down" processing, may also be caused by damage to the "bottom-up," more elementary sensory processes.

Finally, Freyberger [31] has proposed to consider secondary alexithymia as stress reaction. In other words, secondary alexithymia is a coping mechanism which aims at protecting the self against emotional distress associated with situations of intense vulnerability [32].

Before proceeding to the main findings of the review, we have considered as necessary to provide some additional information for the reader regarding important issues relating to alexithymia such as its rapport to psychopathy, the possibility to represent a personality trait, and humor styles, as well as a potentially shared cognitive architecture for alexithymia and humor.

2.1. Alexithymia and Psychopathy. Starting from the observation of Apfel and Sifneos [33] that some individuals with alexithymia had psychopathic personalities, alexithymia has been typically associated with both violence and psychopathy. Hence, although alexithymia is mainly conceptualized as a personality trait and psychopathy as personality disorder, the debate on their rapport is still ongoing. However, we need to be cautious when drawing conclusions regarding such associations. Similar manifestations may be seen in both alexithymia and psychopathy, along with emotional and interpersonal sequels, and deficits in understanding self and others [34]. Moreover, empathy, insight, and introspection are lacking in both alexithymia and psychopathy [11]. However, individuals affected by alexithymia tend to be anxious, over controlled, submissive, boring, ethically consistent, and socially conforming, while people with psychopathy tend to be anxiety-free, dominant, and nonconforming [11]. Furthermore, Lander et al. [35] observed a significant association between alexithymia and secondary psychopathy (also known as "neurotic psychopathy"), but not with primary psychopathy (i.e., inability to form emotional bonds with others and a fear insensitivity). The authors interpreted this association in a twofold way: (a) emotional disregulation linking both clinical conditions and (b) failing in control of impulsivity and anxiety [35]. However, there is evidence that an emotional regulation deficit in people with alexithymia results from a cognitive processing failure, while in psychopathic people from a failure to experience emotional arousal, anxiety, and fear in particular, even if they are able to shallowly or hollowly pantomime related feelings [36, 37].

The first description of acquired psychopathy, as suggested by Damasio [38], draws back in the classical description of Phineas Gage by Harlow in 1848, following damage to the orbitofrontal cortex (OFC). Later studies on patients with OFC damage showed a close resemblance to psychopathy, called pseudopsychopathy [39], and later to acquired sociopathy [38]. However, Hornak et al. [40] suggested that the OFC damage needs to be bilateral and rather extensive to cause changes in social behavior, while, according to Hare [41], the inability of such patients to make longer-term plans (dysexecutive problems) may be accounted for and, consequently, their manifestations do not directly correspond to psychopathic tendencies. Jurado and Junque [42] also reported two patients who presented personality changes consistent with dissociability, including delinquency, as a result of an OFC lesion. Blair and Cipollitti [43] described a patient presenting acquired sociopathy (i.e., pseudosociopathy) following trauma to the right frontal region, including the OFC, and suggested that his reduced ability to generate expectations of others' negative emotional reactions, particularly anger, may account for his sociopathic manifestations. Müller et al. [44] reported two detained sexual offenders with personality disorder and posttraumatic pseudosociopathy after frontal lobe damage. Both did not have identifiable MRI evidence of structural damage but had decreased glucose metabolism in the left frontobasal and basal ganglia regions in the former, and in the right prefrontal and right insular cortices in the latter, as suggested by PET scan.

2.2. Is Alexithymia a Personality Trait? Another conflicting topic is whether alexithymia constitutes a personality trait or a distinct nosographic entity. A number of leading authors have suggested that alexithymia represents a relatively stable personality trait predisposing people to develop psychopathology, while the supposed characterologic stability becomes accentuated by the state of illness, returning to preexisting conditions after the dissipation of symptoms [45–47]. However, the stability hypothesis cannot represent a conclusive finding supporting alexithymia as a personality trait, since it cannot tell us about the premorbid levels of alexithymia in patients suffering mental illness. Due to the considerable overlap between alexithymia and anxiety and depression symptoms occurring in patients with affective disorders [48], future studies evaluating alexithymia among psychiatric populations should control for the severity of anxiety and depression before concluding that alexithymia is a personality trait predisposing to mental disorders.

2.3. Cognitive Psychology of Humor. At a cognitive level, the potential overlap between humor processing and alexithymia may be ascribed to processes both related to abstract thinking, mental flexibility, individual memory, and interoceptive awareness.

Although humor appreciation requires the conjunct contribution of higher level cognitive processes and affective responsiveness, the specific cognitive operations required to understand humor include abstract reasoning, cognitive flexibility, and effective memory. In order to understand humor, the ability to disregard the literal meaning and to derive a deeper-extended meaning from what is not explicitly stated is required [49]. Moreover, there is evidence for a theoretical relationship between sense of humor and cognitive flexibility [50]. Humor is a coping strategy implying positive reappraisal and processing of witty verbal expressions which allows people to distance themselves from stressful events or situations, thus gaining perspective [51]. Psychological inflexibility can be thought of as being excessively entangled in experiential avoidance and cognitive fusion. A link between alexithymia and psychological inflexibility has been hypothesized, by focusing on the latter as a sort of inability in choosing behavior in line with identified values and goals due to difficulties in connecting with the present moment fully, and blindly sticking to rigid rules [52, 53]. Additionally, cognitive flexibility may also be conceived in terms of thought styles, such as lateral thinking as opposed to vertical thinking, convergent thinking as opposed to divergent thinking, and complexity as opposed to rigidity [54].

Of importance to our discussion on the mental operations involved in humor processing is the incongruity resolution theory [55–57], based on the discrepancy between abstract ideas and real things. The resolution phase is thought to be a problem-solving operation, an effort to draw information or inferences leading to the detection of a link or a fit between the initial body of the humoristic stimulus and its ending.

2.4. Right Hemisphere and Individual Memory. Individual memory, meaning memory for subjective states and orientation to self and surroundings, may be disturbed following right hemisphere lesions, against a background of intact verbal and logical memory [58, 59]. This finding stemming from the classical work of Luria seems comparable to some extent with recent evidence linking right hemisphere damage to the manifestation of secondary alexithymia [16], since the right hemisphere has been extensively conceptualized as being devoted to emotional processing.

2.5. The Role of Interoceptive Awareness. Interoceptive awareness is also linked to emotional and social cognition. Quite recently, interoception has been conceptualized within a predictive coding framework [60]. The predictive coding framework states that resourcing to previously encode internal sensory cues is imperative for linking personal emotional state to external events. Impairments in predicting internal sensations may hinder the formation of associations between those sensations and salient social or emotional external events, possibly contributing to social and communication failures. Chronic abnormalities in interoceptive predictive coding may progressively lead to a sort of blindness for interoceptive cues, which become then habitually disregarded, and consequently giving rise to a pathological feedback loop (e.g., impaired attention makes cues less predictive, which then reinforces inattention). Such difficulties are encountered in people in the autistic spectrum, manifesting difficulty using prior sensory experience to make accurate predictions of future sensory events [61]. The neuroanatomy of interoceptive inference has been mapped onto several neuroanatomical substrates, such as the anterior insular cortex (AIC), ACC, the subgenual cortex (SGC), and OFC. Thus, interoceptive awareness represents a further cognitive aspect of secondary alexithymia, since the insular cortex is particularly involved in interoceptive processing.

2.6. Humor Styles. Relative to the humor styles, their original conception is ascribed to the Humor Styles Questionnaire (HSQ) measuring two main factors involved in humor: one used to enhance the self or one's relationships with others and another suggesting whether humor is relatively benevolent or potentially detrimental and destructive. The combination of these factors gives rise to four different humor styles: affiliative (jokes everyone might find funny), self-enhancing (find the humor in everyday situations as a copying strategy), aggressive (put-downs or insults targeted toward individuals), and self-defeating (an unhealthy form of humor, also implemented as a bullying avoidance strategy) [62].

3. Materials and Methods

A systematic narrative review was conducted in compliance with PRISMA guidelines [63]. The time period searched was 1970 to 2017 using the National Library of Medicine PubMed database (http://pubmed.gov) and Medscape.

The search keywords were "organic," "acquired," "primary," "secondary," "humor" AND "detection" OR "appreciation," AND "styles," AND "traumatic," "brain," "injury," "psychopathy" AND "personality" AND "trait," "psychopathy," "memory," "interoception," "flexibility," "cognitive" AND "psychological" AND "processing," "abstract" AND "thinking" AND "reasoning," "incongruity" AND "resolution," "inference," "inflexibility," "neurological" AND "disorders," "diagnostic" AND "classification," "hemispheric" AND "asymmetry," "neuroanatomy," "neuroimaging," "electrophysiology," "neurophysiology." A combined search of the above terms with the term "alexithymia" has been undertaken.

From the above search, 1346 articles were identified, 98 of which were included/selected for this review. The inclusion criteria for the selection were based on the preestablished inclusion criteria (see below) and studies relative to the review topic reported within the initially identified papers (Figure 1).

4. Inclusion Criteria

Studies needed to comply with the following criteria to be included in the review:

(1) The sample consisted of adult participants only (i.e., the mean or median age of the sample was equal to or above 18 years)

(2) Since secondary alexithymia is a less studied topic and as such has been investigated by fewer studies,

Figure 1: PRISMA flow diagram. The flow diagram depicts the flow of information through the different phases of a systematic review.

we used neurobiological evidence deriving from both secondary and acquired cases, and occasionally, from congenital alexithymia cases. Though further research is warranted to clarify if secondary alexithymia should be considered as a separate clinical entity, as suggested by Messina et al. [10], hereby we use the expression "alexithymia" under the rubric of secondary alexithymia

(3) The great majority of studies of either secondary or congenital alexithymia have implemented the 20-Item Toronto Alexithymia Scale (TAS-20) to diagnose the presence of alexithymia symptoms by administering it to patients and matched controls, or to patients only

(4) In our work, only peer-reviewed journal papers written in English have been considered, except for the inclusion of three German articles (reported in the identified English language literature)

(5) Neuroimaging studies were included in this review whenever they were suggested by the identified literature using the abovementioned methods and inclusion criteria

5. Results

5.1. Alexithymia Studies

5.1.1. Neuroradiological and Electrophysiological Evidence. It has been assumed that a pool of anterior brain structures, i.e., PFC, ACC, frontostriatal network, insula, amygdala, corpus callosum, and anterior commissure, plays an important role in emotional processing and expression in primary alexithymia [64]. Berthoz et al. [65] sustained that alexithymia, as a deficit of higher order appraisal of emotional stimuli, may be linked to the ACC and mediofrontal cortex (mFC) malfunction, while amygdalar, hippocampal, and hypothalamic processing links to lower order aspects of emotional stimuli (i.e., the perceptual information of Reiman et al. [66]), remain intact.

Furthermore, these authors observed that the modulation of ACC and mFC activity caused by the emotional valence of stimuli was aberrant in alexithymic subjects, showing activity reduction and increase toward intense negative and positive stimuli, respectively [65]. The authors concluded that primary alexithymia reveals itself by exacerbating personality traits, and usually plays a role in affect regulation associated with circumscribed valence-dependent differences in

the activity of ACC and mFC during emotional stimuli processing [65].

Lane et al. [15] proposed an ACC damage hypothesis (the blind-feel hypothesis), linking alexithymia to ACC activity deficit during states of emotional arousal. In particular, they regard alexithymia as a deficit in the conscious self-awareness of emotions and postulate that a neural disconnection mechanism prevents interoceptive information from adequately informing cortical regions, including ACC. In their positron emission tomography (PET) study, the authors reported a strong correlation between emotional arousal and the flow of blood in the anterior cingulate cortex. Evidence pointing to the same direction concerns the relation between low oxygen pressure, reflected in the low hemoglobin levels of oncologic patients, and alterations in ACC functioning [67]. Furthermore, other PET studies showed not only lower activation rates in the right orbital-PFC [68], as well as in the right frontal areas, but also higher activation rates in the left frontal cortices during recall of autobiographic emotional information [69] in alexithymic individuals as compared to those in healthy individuals.

A deregulation of emotional appraisal processes in congenital alexithymia was suggested by electrophysiological studies detecting a decrease of the upper theta band over the left frontal cortex during responses to emotional stimuli [70].

In sum, the relationship between primary alexithymia and the PFC activity has not yet been adequately addressed and it seems to be still somewhat equivocal.

5.1.2. Frontostriatal and Limbic Contributions to Alexithymia. Since the striato-thalamo-cortical circuitry is likely to support emotional processing [71], various structures involved in that circuitry, such as the globus pallidus, ventral striatum, and caudate and subthalamic nuclei have been linked to both congenital [72] and secondary alexithymia [9]. There is evidence suggesting lower right caudate nucleus activation in response to angry facial stimuli even among healthy individuals with high levels of alexithymic traits [73].

A severe and resistant form of secondary alexithymia associated with bilateral globus pallidus hypoxic brain damage after carbon monoxide poisoning has been reported [9], as well as emotional awareness impairment following globus pallidus anoxic lesion [74].

The amygdala and its projections to subcortical structures, i.e., the hypothalamus, the hippocampus, and the red nucleus of the stria terminalis; the preoptic area; and the periaqueductal grey matter [75], make up a network assumed to be a phylogenetically ancient system for emotional regulation. The amygdala mediates both inborn emotional and acquired behaviors [76], while the prefrontal cortex, especially the orbital and medial portions, is related to emotional feeling which in turn links to some extent to emotional reflection [77]. If the medial PFC does not inhibit the amygdala, then the latter would trigger preprogrammed and evolutionary archaic emotional behaviors, rendering emotional feeling and reflection purposeless.

Evidence that aberrant forms of the cognitive processing of emotional information inhibit the impact of such amygdalar inputs led some authors to postulate four different alexithymic personality types within the broader concept of alexithymia [64]. These types may possibly reflect childhood's abnormal experiences, leading the main cerebral components regulating emotional experience, i.e., the amygdala and the prefrontal cortex, to remain functionally fixated at early stages of development. For instance, Patrikelis et al.'s [12] patient (see below) personality type seems compatible with Bermond et al.'s [64] second personality type, described as "…entailing a strong tendency to activate cognitive processing of emotional information modules which inhibit other neural modules involved in emotionalising…", for which persons mainly experience emotionally detached emotion-related cognitions. Unfortunately, Bermond's typology is referred to as primary alexithymia, and it may not be applicable to secondary alexithymia cases, like the abovementioned, at least until a correlation between the alexithymic types and brain structures—or systems—is not revealed. Some authors [20] claimed that the debate on whether the symptoms of secondary alexithymia have different underlying neuronal mechanisms and clinical expressions from those of the nonsecondary one is still ongoing, though secondary alexithymia does not always result as clinically different from primary alexithymia cases. Furthermore, the difficulty in differentiating secondary from nonsecondary alexithymia is due to their shared difficulties in both identifying and verbalizing emotions, as well as the presence of stimulus-bound behavior (concrete and reality-based thinking).

5.1.3. Inflammation and Hormone Imbalances. Research findings likely display a consistency with the "stress-alexithymia hypothesis" [78]. An association between alexithymia and higher circulation levels of acute phase proteins, especially C-reactive protein, has been reported by several studies (e.g., [79]). Moreover, the proinflammatory and anti-inflammatory cytokine balance of alexithymics may be tuned toward a proinflammatory imbalance with a concomitant altered cell-mediated immunity.

Recent studies have associated specific effects of this trait and its subfactors with hypothalamo-pituitary-adrenal (HPA) axis markers during stressful conditions (e.g., [80]). Accordingly, a pioneering study which addressed the putative link between alexithymia and its subfactors on HPA and sympatho-adrenal medullar (SAM) response to healthy controls showed that among all tested stress indicators, cortisol was the only variable positively related to alexithymia, probably pointing to difficulties with the identifying feeling subfactor. Alexithymia was associated with significantly increased cortisol before, during, and after the stress exposure, while no link was found between alexithymia and SAM axis [81].

5.1.4. Alexithymia in Neurological Patients. Although alexithymia is likely to represent a feature of neurological disease, it is not clear how independent it is from other nosological entities, such as depression and anxiety, frequently

encountered as comorbidities in neurological patients. Neurological conditions that received attention for the presence of alexithymia are traumatic brain injuries (TBIs), stroke, epilepsy, and, to a lesser degree, movement disorders and multiple sclerosis. Although there is a relatively high incidence of secondary alexithymia among people who have suffered head injuries (30-40%), the great variability of lesions in TBIs, in terms of location, severity, and extent and the often diffuse nature of axonal injury [82], as well as other methodological issues, e.g., the inability of TBI patients to identify and consequently report their own emotional state by means of self-reported questionnaires [82], make TBIs hard to study.

Williams and Wood [83] have given a possible interpretation for the presence of secondary alexithymia in TBIs suggesting an inverse relationship between alexithymia and emotional empathy. They believe that the capacity for emotional empathy may operate independently of alexithymia after TBI, possibly reflecting the impact of diffuse brain pathology on various emotional circuits, mediated by complex bidirectional and mutually inhibitory interconnections between the ventral prefrontal cortex (VPFC) and the amygdala [84, 85].

Since VPFC is highly vulnerable to the effects of acceleration-deceleration forces in TBIs [86, 87], neural networks responsible for social cognition and cognitive appraisal of stimuli separately from their somatic counterpart and depending on VPFC may be disrupted. This disruption renders patients unable to experience the emotional attributes of stimuli (e.g., Adolphs et al. [88]). Consequently, damage to the VPFC may selectively compromise the ability to recognize one's own emotions and to empathize with others' emotions.

More recently, Hogeveen et al. [89] have suggested that pronounced damage of the anterior insula induces increased levels of alexithymia, providing evidence for a critical role of this region in emotional awareness.

In the context of epilepsy research, alexithymia has been predominantly investigated in patients suffering from psychogenic nonepileptic seizures (PNES), and, to a lesser extent, in patients with epilepsy. Symptoms of psychological trauma and cynicism in patients diagnosed with PNES were associated with alexithymia. These findings are encouraging, as they assist in better understanding the condition and in treatment design for this subset of patients. A recent review [90] reports only two studies presenting alexithymia in conjunction to epilepsy and PNES. The first [91] suggests that "about 30% of both groups scored in the alexithymic range." In contrast, alexithymia in PNES was estimated at around 90.5% and in epilepsy at 76.2% [92]. Myers et al. [90] suggest that alexithymia rates at around 36.9% of their sample with PNES and 28.6% in that with ES and are consistent with the prevalence rates of alexithymia reported in the study by Tojek et al. [91]. They [90] found a positive correlation between alexithymia and heightened symptoms of anxiety and autonomic hyperarousal, intrusive experiences, dissociation, and defensive avoidance, interpreting the above in the light of alexithymia's association with trauma, since the former represents a condition that would be expected to result from physiological and cognitive deregulations following trauma. More specifically, they found an association of alexithymia with psychological trauma and cynicism in PNES patients.

Moreover, few studies taking alexithymia into account have been conducted in the domains of multiple sclerosis and movement disorders [93].

5.2. Humor Processing Studies

5.2.1. Neuroradiological Evidence. The ability to produce and comprehend humor is a critical interpersonal ability in promoting suitable social interactions. Humor processing entails many cognitive aspects, such as (a) the setup of the joke—-associated with temporal lobe (i.e., temporal pole and anterior superior temporal sulcus (aSTS)) activation [94–97]; (b) humor comprehension and detection/resolution of incongruity—involving the inferior frontal gyrus (IFG) [97–100] and regions around the temporal parietal junction (TPJ) [94, 97, 101]; and (c) the attribution of mental states to the characters of the joke related to the activation of the anterior medial prefrontal cortex (amPFC) [102, 103]. Moreover, it could be claimed that affective components of humor processing are related to the medial ventral prefrontal cortex (mvPFC), subcortical nuclei (nucleus accumbens), bilateral insular cortex, and left amygdala functioning [94, 96, 98, 99, 104].

Some studies emphasized cerebral activations in regard to structural elements of humoristic stimuli. Specifically, phonological puns activate areas involved in sound processing, i.e., the left inferior precentral gyrus and insula, whereas semantic jokes activate regions processing word meaning, i.e., the left posterior inferior temporal gyrus (pITG) and the right posterior middle temporal gyrus (pMTG) [98]. Finally, some differences were observed comparing visual-based vs. language-based humor. In brief, the former activates, among others, the bilateral higher-order visual cortex, TPJ, middle frontal gyrus (MFG), and precuneus, while the latter specifically activates the MTG, IFG, and ITG [100].

According to Moran et al. [96], the neural underpinnings of humor detection and appreciation are functionally separable, with the posterior temporal and inferior frontal regions devoted to resolving contextual ambiguities and recruited during humor detection, and the insular cortex implicated in visceral responses characterizing the mirth experience.

5.3. Joint Evidence for Alexithymia and Defective Humor Processing. In a unique behavioral genetic study from Atkinson et al. [105] on the rapport between congenital alexithymia and humor styles, it has been found that positive humor styles correlated negatively with alexithymia, while maladaptive humor styles (self-defeating and aggressive humor) correlated positively with alexithymia. Phenotypic correlations between alexithymia and humor styles were primarily attributable to associated genetic factors and, to a lesser extent, to nonshared environmental factors. A possible reason accounting for correlations between humor styles and alexithymia in the above study is that both correlate with empathy. Affiliative humor (i.e., positively involving others

Table 1: Secondary alexithymia and humor studies.

Organic alexithymia		Aberrant humor	
Studies	Brain region	Brain region	Studies
Paradiso et al., [74] Messina et al., [67] Patrikelis et al., [12] Hobson et al., [26] Schäfer et al., [29]	Ventral-rostral ACC/*mPFC*	*IFG*, *MFG*, ITG MTG, TPJ, and precuneus	Watson et al., [100]
		IFG	Wild et al., [97] Goel and Dolan, [98] Bartolo et al., [99] Watson et al., [100]
		mvPFC	Mobbs et al., [94] Moran et al., [96] Goel and Dolan, [98] Bartolo et al., [99] Sieboerger et al., [104]
		amPFC	Gallagher et al., [102] Marjoram et al., [103]
Hogeveen et al., [89]	*Anterior insula*	*Insula*	Moran et al., [96]
		Insula, left IPG, left pITG, and right pMTG	Goel and Dolan, [98]
Hoppe and Bogen, [13] Galin, [14]	*Corpus callosum*		
Huang et al., [9] Paradiso et al., [74]	*Globus pallidus*		
Spalletta et al., [16] Ho and Lee [30] Schäfer et al., [29]	*Right hemisphere*		
Williams et al., [83]	*Bilateral frontal and parietal lobes*	Insula, *left IPG*, *left pITG*, and *right pMTG*	Goel and Dolan, [98]

and enhancing social interaction) and self-enhancing humor (i.e., enhancing the self) show a significantly positive correlation with empathy [106] that in turn is negatively correlated with alexithymia [107]. Moreover, a negative correlation between aggressive humor and empathy has been reported [106]. With regards to the neural underpinnings of empathy, it has been observed that perceiving and assessing painful situations experienced by others induce significant bilateral changes in the anterior cingulate, the anterior insula, the cerebellum, and, to a lesser extent, the thalamus, structures known for playing a significant role in pain processing [108].

A recent case study described a patient who was operated for a huge frontal-groove meningioma that presented with secondary alexithymia and impaired humor appreciation as the result of damage to the ventral-rostral portions of the anterior cingulate gyrus/mPFC, which prevented the patient from assessing the salience of emotion and motivational information and generating emotional reactions; consequently, he had difficulties in experiencing emotions, knowing how he and others feel, and enjoying humor [12] (Table 1).

However, evidence on secondary alexithymia and its relation with humor deficits is scarce and even absent.

6. Discussion

By drawing upon evidence from current literature and expert opinion derived from clinical practice, we suggest that clinicians and researchers working in the area of neurology, psychiatry, and clinical neurosciences should be aware of the putative link between secondary alexithymia and abnormal humor processing. Increased awareness on this topic may aid neurosurgeons when accessing emotion-relevant structures, as well as clinical neuropsychologists to plan evidence-based neurorehabilitative interventions in order to alleviate the deleterious effects of such interpersonal communication deficits.

Secondary alexithymia may be viewed as a specific variant of secondary alexithymia resulting from damage in specific brain regions including the ACC, basal ganglia, insula, right hemisphere, and corpus callosum [10], particularly those mediating emotional awareness or linking somatic signals to their abstract linguistic-symbolic counterparts. However, to our knowledge, the study of a possible common neurological link between alexithymia and aberrant humor processing has not yet been systematically addressed, and has been limited mainly to single-case study observations [12] or even to anecdotal evidence.

On the other hand, humor detection and appreciation are dissociable processes from both functional and structural points of view, with the posterior temporal and inferior frontal regions recruited during humor detection in order to resolve contextual ambiguities and the insula implicated in visceral responses characterizing the mirth experience [96]. Furthermore, limbic regions involved in generating emotional responses (i.e., amygdala, nucleus accumbens, hypothalamus, and anterior insula) are regulated by the ventral ACC/mPFC. The amygdala mediates both inborn emotional and acquired behaviors [76], while the PFC, specifically its orbital and medial portions, is related to emotional feeling which in turn encompasses to some extent emotional reflection. Disconnections between the mPFC and the above

limbic components may thus produce a state of humor appreciation deficit, a sort of humor anhedonia.

In summary, what emerges from the literature is that the cortical midline structures, in particular the mPFC, ACC, and insular cortex, seem to play a crucial role in the expression of both alexithymia and defective humor processing, while to a lesser extent, a right hemisphere and bilateral frontoparietal contribution becomes evident. Consistently, a recent theory assumes that neural activity in the anterior cortical midline structures is critical for emotional feeling [109], while focal node dysfunction within the emotional processing networks may lead to selective patterns of neurobehavioral impairments, often leading to a more generalized network malfunction. Taken together, neurobiological evidence of secondary alexithymia and aberrant humor processing points to the putative role of ACC/mPFC and the insula in representing crucial processing nodes whose damage may produce both the above clinical conditions. We believe that the association of secondary alexithymia and aberrant humor processing, especially humor appreciation deficit, and their association with specific brain regions, mainly ACG/mPFC and the insular lobe, as emerged from the literature, may be of some heuristic importance.

We speculate that the above neuroanatomical findings linked to the expression of secondary alexithymia may be conceptualized as a possible breakdown of a network subserving integration of interoceptive, affective, and linguistic information. In terms of the Lurian model of brain function, the emergent lesional pattern (in particular, ACC/mPFC and the insula) leads us to hypothesize a possible disruption of the functional interplay between the first and the second functional blocks, as suggested by Luria's functional brain model [110]. The first block (in our case ACG/mPFC) is mediated by the reticular formation and the medial surface of the cerebral hemispheres, while the second (in our case insula) relies on the association cortices. In the light of this model, we assume that a disruption could occur at any level of information processing, normally taking place due to the cooperation of the above functional blocks.

This is quite crucial in neurosurgery, when the surgeon has to deal with brain pathologies related mainly with ACC and mPFC, such as brain tumors (meningiomas, gliomas), trauma (cerebral contusions), and stroke (infarctions, hemorrhages). Patients may present signs of secondary alexithymia and aberrant humor processing even before the operation, and consequently presurgical planning should include detailed neuropsychological assessment and functional neuroimaging. Intraoperatively, the neurosurgeon should protect the ACC and mPFC areas, as far as possible, in order to minimise further parenchymal damage of eloquent brain areas and consequently to avoid postoperative neuropsychological deterioration, which will make the patient's postoperative neurorehabilitation and therapeutic outcome more complex.

Moreover, increased awareness of the frequent coexistence between secondary alexithymia and humor appreciation deficit, and most importantly their shared neurobiological and cognitive underpinnings may provide a direct aid in the context of neuropsychological rehabilitation. Neurobiological (e.g., MRI and PET scans) and neurocognitive (e.g., patterns of cognitive dysfunction pointing to mental flexibility and abstract reasoning problems) evidence seen in the light of our review results may be informative with respect to the breakdown of affected neural tissues and cognitive processes and their coproducts, and consequently determine which of them should be targeted in the course of the neurorehabilitation program. In particular, mental flexibility, abstract verbal reasoning, interoceptive awareness, and right hemisphere function should be taken into consideration whenever dealing with such patients.

Psychiatrists may target neurotransmission systems linked to the emotionally relevant structures playing a decisive role in both the expression of secondary alexithymia and humor appreciation, by drawing on the anatomical distribution of abnormal imaging findings and the neurocognitive architecture of such neurobehavioral breakdowns.

Future studies should target the rapport of secondary alexithymia with humor processing by focusing on the analysis of lesions' anatomical site, extent and severity, and underlying pathophysiology, as well as patients' cognitive and psychosocial parameters. Once such issues are resolved, clinicians in the context of neuropsychological rehabilitation will be able to precisely map cognitive and affective impairments (e.g., humor appreciation deficit) and their dynamic interactions, and consequently plan effective neurorehabilitative programs to address the kaleidoscopic nature of problems in secondary alexithymia.

7. Conclusion

It appears that a selective involvement of the anterior cortical midline structures (mFC, ACC, and the insula, in particular) is likely to reflect the pathophysiological underpinnings of both secondary alexithymia and humor appreciation deficit. From a cognitive point of view, abstract thinking, mental flexibility, individual memory, and interoceptive awareness are the likely candidates for cognitive rehabilitation interventions in patients suffering secondary alexithymia and/or humor appreciation deficit. Finally, we hypothesize that functional breakdowns in integrating interoceptive, affective, and linguistic information may be responsible for the expression of secondary alexithymia and humor appreciation deficit, while the disruption could occur at any level of information processing, normally taking place within the domain of the Lurian first and second functional blocks.

Conflicts of Interest

The authors report no conflicts of interest.

References

[1] G. J. Taylor, "Recent developments in alexithymia theory and research," *Canadian Journal of Psychiatry*, vol. 45, no. 2, pp. 134–142, 2000.

[2] G. J. Taylor, R. M. Bagby, and J. D. A. Parker, *Disorders of Affect Regulation. Alexithymia in Medical Psychiatric Illness*, Cambridge University Press, UK, 1997.

[3] F. Leweke, F. Leichsenring, J. Kruse, and S. Hermes, "Is alexithymia associated with specific mental disorders?," *Psychopathology*, vol. 45, no. 1, pp. 22–28, 2012.

[4] A. Carano, D. de Berardis, F. Gambi et al., "Alexithymia and body image in adult outpatients with binge eating disorder," *The International Journal of Eating Disorders*, vol. 39, no. 4, pp. 332–340, 2006.

[5] M. Y. Güleç, L. Ýnanç, Ö. Yanartaþ, A. Üzer, and H. Güleç, "Predictors of suicide in patients with conversion disorder," *Comprehensive Psychiatry*, vol. 55, no. 3, pp. 457–462, 2014.

[6] D. De Berardis, M. Fornaro, L. Orsolini et al., "Alexithymia and suicide risk in psychiatric disorders: a mini-review," *Frontiers in Psychiatry*, vol. 8, p. 148, 2017.

[7] D. De Berardis, N. Serroni, S. Marini et al., "Alexithymia, suicidal ideation, and serum lipid levels among drug-naïve outpatients with obsessive-compulsive disorder," *Revista Brasileira de Psiquiatria*, vol. 36, no. 2, pp. 125–130, 2014.

[8] J. D. Henry, L. H. Phillips, J. R. Crawford, G. Theodorou, and F. Summers, "Cognitive and psychosocial correlates of alexithymia following traumatic brain injury," *Neuropsychologia*, vol. 44, no. 1, pp. 62–72, 2006.

[9] M. F. Huang, Y. C. Yeh, H. Y. Tsang, and C. S. Chen, "Alexithymia associated with bilateral globus pallidus lesions after carbon monoxide poisoning," *The Kaohsiung Journal of Medical Sciences*, vol. 26, no. 6, pp. 333–336, 2010.

[10] A. Messina, J. N. Beadle, and S. Paradiso, "Towards a classification of alexithymia: primary, secondary and organic," *Journal of Psychopathology*, vol. 20, pp. 38–49, 2014.

[11] M. G. Haviland, J. L. Sonne, and P. A. Kowert, "Alexithymia and psychopathy: comparison and application of California Q-set prototypes," *Journal of Personality Assessment*, vol. 82, no. 3, pp. 306–316, 2004.

[12] P. Patrikelis, G. Konstantakopoulos, G. Lucci et al., "Possible common neurological breakdowns for alexithymia and humour appreciation deficit: a case study," *Clinical Neurology and Neurosurgery*, vol. 153, pp. 1–4, 2017.

[13] K. D. Hoppe and J. E. Bogen, "Alexithymia in twelve commissurotomized patients," *Psychotherapy and Psychosomatics*, vol. 28, no. 1-4, pp. 148–155, 1977.

[14] D. Galin, "Implications for psychiatry of left and right cerebral specialization: a neurophysiological context for unconscious processes," *Archives of General Psychiatry*, vol. 31, no. 4, pp. 572–583, 1974.

[15] R. D. Lane, G. L. Ahern, G. E. Schwartz, and A. W. Kaszniak, "Is alexithymia the emotional equivalent of blindsight?," *Biological Psychiatry*, vol. 42, no. 9, pp. 834–844, 1997.

[16] G. Spalletta, A. Pasini, A. Costa et al., "Alexithymic features in stroke: effects of laterality and gender," *Psychosomatic Medicine*, vol. 63, no. 6, pp. 944–950, 2001.

[17] E. D. Ross, R. W. Homan, and R. Buck, "Differential hemispheric lateralization of primary and social emotions," *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, vol. 7, pp. 1–19, 1994.

[18] R. Adolphs, H. Damasio, D. Tranel, and A. R. Damasio, "Cortical systems for the recognition of emotion in facial expressions," *The Journal of Neuroscience*, vol. 16, no. 23, pp. 7678–7687, 1996.

[19] M. Jessimer and R. Markham, "Alexithymia: a right hemisphere dysfunction specific to recognition of certain facial expressions," *Brain and Cognition*, vol. 34, no. 2, pp. 246–258, 1997.

[20] R. Becerra, A. Amos, and S. Jongenelis, "Organic alexithymia: a study of acquired emotional blindness," *Brain Injury*, vol. 16, no. 7, pp. 633–645, 2002.

[21] M. S. Gazzaniga, "Consciousness and the cerebral hemispheres," in *The Cognitive Neurosciences*, M. S. Gazzaniga, Ed., pp. 1391–1401, MIT Press, Cambridge, MA, USA, 1995.

[22] S. Tekin and J. L. Cummings, "Frontal–subcortical neuronal circuits and clinical neuropsychiatry: an update," *Journal of Psychosomatic Research*, vol. 53, no. 2, pp. 647–654, 2002.

[23] Y. I. Sheline, D. M. Barch, J. L. Price et al., "The default mode network and self-referential processes in depression," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 6, pp. 1942–1947, 2009.

[24] S. L. Bressler and V. Menon, "Large-scale brain networks in cognition: emerging methods and principles," *Trends in Cognitive Sciences*, vol. 14, no. 6, pp. 277–290, 2010.

[25] L. Zhang, C. Zhu, R. Ye et al., "Impairment of conflict processing in alexithymic individuals," *Neuroscience Letters*, vol. 504, no. 3, pp. 261–264, 2011.

[26] H. Hobson, J. Hogeveen, R. Brewer et al., "Language and alexithymia: evidence for the role of the inferior frontal gyrus in acquired alexithymia," *Neuropsychologia*, vol. 111, pp. 229–240, 2018.

[27] R. Brewer, R. Cook, and G. Bird, "Alexithymia: a general deficit of interoception," *Royal Society Open Science*, vol. 3, no. 10, p. 150664, 2016.

[28] P. Shah, R. Hall, C. Catmur, and G. Bird, "Alexithymia, not autism, is associated with impaired interoception," *Cortex*, vol. 81, pp. 215–220, 2016.

[29] R. Schäfer, K. Popp, S. Jörgens, R. Lindenberg, M. Franz, and R. J. Seitz, "Alexithymia-like disorder in right anterior cingulate infarction," *Neurocase*, vol. 13, no. 3, pp. 201–208, 2007.

[30] N. S. P. Ho and T. M. C. Lee, "Alexithymia: the story of a survivor of childhood traumatic brain injury," *Brain Injury*, vol. 27, no. 10, pp. 1199–1205, 2013.

[31] H. Freyberger, "Supportive psychotherapeutic techniques in primary and secondary alexithymia," *Psychotherapy and Psychosomatics*, vol. 28, no. 1-4, pp. 337–345, 1977.

[32] D. De Berardis, D. Campanella, N. Serroni et al., "The impact of alexithymia on anxiety disorders: a review of the literature," *Current Psychiatry Reviews*, vol. 4, no. 2, pp. 80–86, 2008.

[33] R. J. Apfel and P. E. Sifneos, "Alexithymia: concept and measurement," *Psychotherapy and Psychosomatics*, vol. 32, no. 1-4, pp. 180–190, 1979.

[34] S. M. Louth, R. D. Hare, and W. Linden, "Psychopathy and alexithymia in female offenders," *Canadian Journal of Behavioural Science*, vol. 30, no. 2, pp. 91–98, 1998.

[35] G. C. Lander, C. J. Lutz-Zois, M. S. Rye, and J. A. Goodnight, "The differential association between alexithymia and primary versus secondary psychopathy," *Personality and Individual Differences*, vol. 52, no. 1, pp. 45–50, 2012.

[36] H. Cleckley, *The Mask of Sanity*, Mosby, St. Louis, MO, USA, 5th edition, 1988.

[37] R. D. Hare, *Without Conscience: The Disturbing World of Psychopaths among Us*, Guilford, New York, NY, USA, 1993.

[38] A. R. Damasio, *Descartes' Error: Emotion, Rationality and the Human Brain*, Putnam, New York, NY, USA, 1994.

[39] D. Blumer and D. F. Benson, "Personality changes with frontal lobe lesions," in *Psychiatric Aspects of Neurological Disease*, D. F. Benson and D. Blumer, Eds., pp. 171–198, Grune & Stratton, New York, NY, USA, 1975.

[40] J. Hornak, J. Bramham, E. T. Rolls et al., "Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices," *Brain*, vol. 126, no. 7, pp. 1691–1712, 2003.

[41] R. D. Hare, "Performance of psychopaths on cognitive tasks related to frontal lobe function," *Journal of Abnormal Psychology*, vol. 93, no. 2, pp. 133–140, 1984.

[42] M. A. Jurado and C. Junque, "Criminal behavior after orbitofrontal lesion," *Actas Españolas de Psiquiatría*, vol. 28, no. 5, pp. 337–341, 2000.

[43] R. J. R. Blair and L. Cipolotti, "Impaired social response reversal: a case of acquired sociopathy," *Brain*, vol. 123, no. 6, pp. 1122–1141, 2000.

[44] J. L. Müller, G. Schuierer, J. Marienhagen, A. Putzhammer, and H. E. Klein, ""Acquired psychopathy" und die neurobiologie von emotion und gewalt," *Psychiatrische Praxis*, vol. 30, pp. 221–225, 2003.

[45] G. J. Taylor and R. M. Bagby, "New trends in alexithymia research," *Psychotherapy and Psychosomatics*, vol. 73, no. 2, pp. 68–77, 2004.

[46] S. Saarijärvi, J. K. Salminen, and T. B. Toikka, "Temporal stability of alexithymia over a five-year period in outpatients with major depression," *Psychotherapy and Psychosomatics*, vol. 75, no. 2, pp. 107–112, 2006.

[47] O. Luminet, R. M. Bagby, and G. J. Taylor, "An evaluation of the absolute and relative stability of alexithymia in patients with major depression," *Psychotherapy and Psychosomatics*, vol. 70, no. 5, pp. 254–260, 2001.

[48] C. Marchesi, E. Brusamonti, and C. Maggini, "Are alexithymia, depression, and anxiety distinct constructs in affective disorders?," *Journal of Psychosomatic Research*, vol. 49, no. 1, pp. 43–49, 2000.

[49] P. Shammi and D. T. Stuss, "Humour appreciation: a role of the right frontal lobe," *Brain*, vol. 122, no. 4, pp. 657–666, 1999.

[50] K. G. F. Esterhuyse, N. Nortjé, A. Pienaar, and R. B. I. Beukes, "Sense of humour and adolescents' cognitive flexibility," *South African Family Practice*, vol. 55, no. 1, pp. 90–95, 2013.

[51] J. Duarte and J. Pinto-Gouveia, "Correlates of psychological inflexibility mediate the relation between alexithymic traits and positive emotions," *Journal of Contextual Behavioral Science*, vol. 6, no. 1, pp. 96–103, 2017.

[52] S. C. Hayes, K. D. Strosahl, and K. G. Wilson, *Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change*, Guilford Press, New York, NY, USA, 1999.

[53] S. C. Hayes, J. B. Luoma, F. W. Bond, A. Masuda, and J. Lillis, "Acceptance and commitment therapy: model, processes, and outcomes," *Behaviour Research and Therapy*, vol. 44, no. 1, pp. 1–25, 2006.

[54] R. J. Sternberg, *The Triarchic Mind: A New Theory of Human Intelligence*, New York, NY, USA, Penguin Group, 1988.

[55] J. M. Jones, *Cognitive Factors in the Appreciation of Humor: A Theoretical and Experimental Analysis*, Unpublished doctoral dissertation, Yale University, 1970.

[56] T. R. Shultz, "The role of incongruity and resolution in children's appreciation of cartoon humor," *Journal of Experimental Child Psychology*, vol. 13, no. 3, pp. 456–477, 1972.

[57] J. Suls, "A two-stage model for the appreciation of jokes and cartoons," in *Psychology of Humor*, J. H. Goldstein and P. E. McGhee, Eds., Academic Press, New York, NY, USA, 1972.

[58] A. R. Luria and E. G. Simernitskaya, "Interhemispheric relations and the functions of the minor hemisphere," *Neuropsychologia*, vol. 15, no. 1, pp. 175–178, 1977.

[59] A. R. Luria, *The Neuropsychology of Memory. Trans B. Haigh*, VH Winston & Sons, 1976.

[60] A. K. Seth and K. J. Friston, "Active interoceptive inference and the emotional brain," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 371, no. 1708, article 20160007, 2016.

[61] A. K. Seth, K. Suzuki, and H. D. Critchley, "An interoceptive predictive coding model of conscious presence," *Frontiers in Psychology*, vol. 2, p. 395, 2012.

[62] R. A. Martin, P. Puhlik-Doris, G. Larsen, J. Gray, and K. Weir, "Individual differences in uses of humor and their relation to psychological well-being: development of the Humor Styles Questionnaire," *Journal of Research in Personality*, vol. 37, no. 1, pp. 48–75, 2003.

[63] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and The PRISMA Group, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *British Medical Journal*, vol. 339, no. 1, article b2535, 2009.

[64] B. Bermond, H. C. M. Vorst, and P. P. Moormann, "Cognitive neuropsychology of alexithymia: implications for personality typology," *Cognitive Neuropsychiatry*, vol. 11, no. 3, pp. 332–360, 2006.

[65] S. Berthoz, E. Artiges, P. F. van de Moortele et al., "Effect of impaired recognition and expression of emotions on frontocingulate cortices: an fMRI study of men with alexithymia," *The American Journal of Psychiatry*, vol. 159, no. 6, pp. 961–967, 2002.

[66] E. M. Reiman, R. D. Lane, G. L. Ahern et al., "Neuroanatomical correlates of externally and internally generated human emotion," *The American Journal of Psychiatry*, vol. 154, no. 7, pp. 918–925, 1997.

[67] A. Messina, A. M. Fogliani, and S. Paradiso, "Alexithymia in oncologic disease: association with cancer invasion and hemoglobin levels," *Annals of Clinical Psychiatry*, vol. 23, no. 2, pp. 125–130, 2011.

[68] M. Kano, S. Fukudo, J. Gyoba et al., "Specific brain processing of facial expressions in people with alexithymia: an $H_2{}^{15}O$-PET study," *Brain*, vol. 126, no. 6, pp. 1474–1484, 2003.

[69] M. Huber, K. Herholz, B. Habedank et al., "Differente muster regionaler hirnaktivitat nach emotionaler stimulation bei alexithymen patienten im vergleich zu normalpersonen: eine positron enemissions tomographische (PET-) studie mit ^{15}O-H_2O und emotionaler stimulierung durch autobiografische erinnerung," *Psychotherapie Psychosomatik und Medizinische Psychologie*, vol. 52, no. 11, pp. 469–478, 2002.

[70] L. I. Aftanas, A. A. Varlamov, N. V. Reva, and S. V. Pavlov, "Disruption of early event-related theta synchronization of human EEG in alexithymics viewing affective pictures," *Neuroscience Letters*, vol. 340, no. 1, pp. 57–60, 2003.

[71] T. Dondaine and J. Péron, "Emotion and basal ganglia (I): what can we learn from Parkinson's disease?," *Revista de Neurologia*, vol. 168, no. 8-9, pp. 634–641, 2012.

[72] H. C. Evrard, T. Forro, and N. K. Logothetis, "Von Economo neurons in the anterior insula of the macaque monkey," *Neuron*, vol. 74, no. 3, pp. 482–489, 2012.

[73] B. T. Lee, H. Y. Lee, S. A. Park et al., "Neural substrates of affective face recognition in alexithymia: a functional magnetic resonance imaging study," *Neuropsychobiology*, vol. 63, no. 2, pp. 119–124, 2011.

[74] S. Paradiso, J. G. Vaidya, L. M. McCormick, A. Jones, and R. G. Robinson, "Aging and alexithymia: association with reduced right rostral cingulate volume," *The American Journal of Geriatric Psychiatry*, vol. 16, no. 9, pp. 760–769, 2008.

[75] J. E. LeDoux, "Emotion circuits in the brain," *Annual Review of Neuroscience*, vol. 23, no. 1, pp. 155–184, 2000.

[76] S. Iversen, I. Kupfermann, and E. R. Kandel, "Emotional states and feelings," in *Principles of Neural Science, fourth ed.*, E. R. Kandel, J. H. Schwartz, and T. M. Jessell, Eds., McGraw-Hill, New York, NY, USA, 2000.

[77] A. R. Damasio, *The Feeling of What Happens: Body, Emotion and the Making of Consciousness*, Heinemann, London, 1999.

[78] J. B. Martin and R. O. Pihl, "The stress-alexithymia hypothesis: theoretical and empirical considerations," *Psychotherapy and Psychosoma-tics*, vol. 43, no. 4, pp. 169–176, 1985.

[79] D. De Berardis, N. Serroni, D. Campanella et al., "Alexithymia and its relationships with C-reactive protein and serum lipid levels among drug naïve adult outpatients with major depression," *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 32, no. 8, pp. 1982–1986, 2008.

[80] E. A. Härtwig, S. Aust, and I. Heuser, "HPA system activity in alexithymia: a cortisol awakening response study," *Psychoneuroendocrinology*, vol. 38, no. 10, pp. 2121–2126, 2013.

[81] J. Hua, C. Le Scanff, J. Larue et al., "Global stress response during a social stress test: impact of alexithymia and its subfactors," *Psychoneuroendocrinology*, vol. 50, pp. 53–61, 2014.

[82] L. Ricciardi, B. Demartini, A. Fotopoulou, and M. J. Edwards, "Alexithymia in neurological disease: a review," *The Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 27, no. 3, pp. 179–187, 2015.

[83] C. Williams and R. L. Wood, "Alexithymia and emotional empathy following traumatic brain injury," *Journal of Clinical and Experimental Neuropsychology*, vol. 32, no. 3, pp. 259–267, 2010.

[84] R. Adolphs, S. Baron-Cohen, and D. Tranel, "Impaired recognition of social emotions following amygdala damage," *Journal of Cognitive Neuroscience*, vol. 14, no. 8, pp. 1264–1274, 2002.

[85] D. D. Dougherty, S. L. Rauch, T. Deckersbach et al., "Ventromedial prefrontal cortex and amygdala dysfunction during an anger induction positron emission tomography study in patients with major depressive disorder with anger attacks," *Archives of GeneralPsychiatry*, vol. 61, no. 8, pp. 795–804, 2004.

[86] J. H. Adams, D. I. Graham, L. S. Murray, and G. Scott, "Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases," *Annals of Neurology*, vol. 12, no. 6, pp. 557–563, 1982.

[87] N. A. Shaw, "The neurophysiology of concussion," *Progress in Neurobiology*, vol. 67, no. 4, pp. 281–344, 2002.

[88] R. Adolphs, D. Tranel, H. Damasio, and A. Damasio, "Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala," *Nature*, vol. 372, no. 6507, pp. 669–672, 1994.

[89] J. Hogeveen, G. Bird, A. Chau, F. Krueger, and J. Grafman, "Acquired alexithymia following damage to the anterior insula," *Neuropsychologia*, vol. 82, pp. 142–148, 2016.

[90] L. Myers, B. Matzner, M. Lancman, K. Perrine, and M. Lancman, "Prevalence of alexithymia in patients with psychogenic non-epileptic seizures and epileptic seizures and predictors in psychogenic non-epileptic seizures," *Epilepsy & Behavior*, vol. 26, no. 2, pp. 153–157, 2013.

[91] T. M. Tojek, M. Lumley, G. Barkley, G. Mahr, and A. Thomas, "Stress and other psychosocial characteristics of patients with psychogenic nonepileptic seizures," *Psychosomatics*, vol. 41, no. 3, pp. 221–226, 2000.

[92] J. Bewley, P. N. Murphy, J. Mallows, and G. A. Baker, "Does alexithymia differentiate between patients with nonepileptic seizures, patients with epilepsy, and nonpatient controls?," *Epilepsy & Behavior*, vol. 7, no. 3, pp. 430–437, 2005.

[93] I. Trinkler, L. Cleret de Langavant, and A. C. Bachoud-Lévi, "Joint recognition expression impairment of facial emotions in Huntington's disease despite intact understanding of feelings," *Cortex*, vol. 49, no. 2, pp. 549–558, 2013.

[94] D. Mobbs, M. D. Greicius, E. Abdel-Azim, V. Menon, and A. L. Reiss, "Humor modulates the mesolimbic reward centers," *Neuron*, vol. 40, no. 5, pp. 1041–1048, 2003.

[95] D. Mobbs, C. C. Hagan, E. Azim, V. Menon, and A. L. Reiss, "Personality predicts activity in reward and emotional regions associated with humor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 45, pp. 16502–16506, 2005.

[96] J. M. Moran, G. S. Wig, R. B. Adams Jr., P. Janata, and W. M. Kelley, "Neural correlates of humor detection and appreciation," *NeuroImage*, vol. 21, no. 3, pp. 1055–1060, 2004.

[97] B. Wild, F. A. Rodden, A. Rapp, M. Erb, W. Grodd, and W. Ruch, "Humor and smiling: cortical regions selective for cognitive, affective, and volitional components," *Neurology*, vol. 66, no. 6, pp. 887–893, 2006.

[98] V. Goel and R. J. Dolan, "The functional anatomy of humor: segregating cognitive and affective components," *Nature Neuroscience*, vol. 4, no. 3, pp. 237-238, 2001.

[99] A. Bartolo, F. Benuzzi, L. Nocetti, P. Baraldi, and P. Nichelli, "Humor comprehension and appreciation: an fMRI study," *Journal of Cognitive Neuroscience*, vol. 18, no. 11, pp. 1789–1798, 2006.

[100] K. K. Watson, B. J. Matthews, and J. M. Allman, "Brain activation during sight gags and language-dependent humor," *Cerebral Cortex*, vol. 17, no. 2, pp. 314–324, 2007.

[101] A. C. Samson, C. F. Hempelmann, O. Huber, and S. Zysset, "Neural substrates of incongruity-resolution and nonsense humor," *Neuropsychologia*, vol. 47, no. 4, pp. 1023–1033, 2009.

[102] H. L. Gallagher, F. Happé, N. Brunswick, P. C. Fletcher, U. Frith, and C. D. Frith, "Reading the mind in cartoons and stories: an fMRI study of "theory of mind" in verbal and nonverbal tasks," *Neuropsychologia*, vol. 38, no. 1, pp. 11–21, 2000.

[103] D. Marjoram, D. E. Job, H. C. Whalley et al., "A visual joke fMRI investigation into theory of mind and enhanced risk of schizophrenia," *NeuroImage*, vol. 31, no. 4, pp. 1850–1858, 2006.

[104] F. T. Sieboerger, E. C. Ferstl, B. Volkmann, and D. Y. von Cramon, *Spaß beiseite! Eine fMRT-Studie und eine behaviorale Patientenstudie zu verbalemHumor und sprachlicher. Revision*, Jahrestagung der Gesellschaft fürNeuropsychologie, München, Germany, 2004.

[105] B. E. Atkinson, D. Lipton, H. M. Baughman, J. A. Schermer, J. Harris, and P. A. Vernon, "How do emotional restrictions affect the use of humor? A behavior genetic analysis of alexithymia and humor styles," *Twin Research and Human Genetics*, vol. 18, no. 2, pp. 138–141, 2015.

[106] W. P. Hampes, "The relation between humor styles and empathy," *Europe's Journal of Psychology*, vol. 6, no. 3, pp. 34–45, 2010.

[107] M. Cairncross, L. Veselka, J. A. Schermer, and P. A. Vernon, "A behavioral genetic analysis of alexithymia and the dark triad traits of personality," *Twin Research and Human Genetics*, vol. 16, no. 3, pp. 690–697, 2013.

[108] P. L. Jackson, A. N. Meltzoff, and J. Decety, "How do we perceive the pain of others? A window into the neural processes involved in empathy," *NeuroImage*, vol. 24, no. 3, pp. 771–779, 2005.

[109] A. Heinzel, S. Moerth, and G. Northoff, "The central role of anterior cortical midline structures in emotional feeling and consciousness," *Psyche*, vol. 16, no. 2, pp. 23–47, 2010.

[110] A. R. Luria, *An Introduction to Neuro-Psychology. Basic Book*, New York Basic Books: A Member of the Perseus Books Publishing, 1973.

Hindawi
Behavioural Neurology
Volume 2019, Article ID 3151092, 6 pages
https://doi.org/10.1155/2019/3151092

Review Article

Cognitive Rehabilitation of Acquired Calculation Disturbances

Alfredo Ardila[1,2] **and Monica Rosselli**[3]

[1]*Florida International University, Miami, FL, USA*
[2]*Sechenov University, Moscow, Russia*
[3]*Florida Atlantic University, Davie, FL, USA*

Correspondence should be addressed to Alfredo Ardila; ardilaalfredo@gmail.com

Received 24 January 2019; Revised 27 February 2019; Accepted 6 March 2019; Published 4 April 2019

Guest Editor: Lambros Messinis

Copyright © 2019 Alfredo Ardila and Monica Rosselli. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Acalculia is an acquired disorder in calculation abilities, usually associated with left posterior parietal damage. Two types of acalculic disorders are usually distinguished: (1) primary acalculia or anarithmetia, where the patient presents a loss of numerical concepts (difficulties are observed both in oral and written calculations), and (2) secondary acalculia due to a different disturbance in cognition and affecting mathematical abilities. Secondary acalculias are associated with aphasia, alexia, agraphia, executive function disorders, or visuospatial difficulties. This paper is a proposal for clinical intervention to rehabilitation of acquired primary and secondary acalculias.

1. Introduction

The disturbance in understanding the numerical system associated with the loss of the ability to perform arithmetical operations is known as *acalculia* (or acquired dyscalculia) [1]. Hence, acalculia is an acquired disturbance, whereas *developmental dyscalculia* or simply *dyscalculia* represents a defect in the ability to normally develop numerical skills [2].

The term "acalculia" was coined by Henschen [3] and defined it as an alteration in mathematical abilities resulting from brain damage. Before Henschen, calculation disturbances were considered to be a component of the acquired language disturbances (aphasias). Later on, Berger [4] proposed a basic distinction between *primary acalculia* and *secondary acalculia*. Ultimately, acalculia can represent a fundamental acquired cognitive disturbance (primary acalculia), but difficulties in performing arithmetical operations can also be found in cases of disturbances in language, attention, reading, writing, and other cognitive impairments (secondary acalculias). Primary acalculia consequently corresponds to a disturbance in understanding numerical concepts and the inability to perform arithmetic operations. Consequently, difficulties are observed both in oral and written calculations. Secondary acalculia is understood as a deficit in numerical abilities due to a different intellectual impairment. Gerstmann [5] suggested that primary acalculia is found associated with agraphia, right-left disorientation, and digital agnosia (inability to recognize the fingers) resulting in a single clinical syndrome that has since become known as "Gerstmann's syndrome" or "angular gyrus syndrome." Rusconi et al. [6] proposed that Gerstmann's syndrome probably arises from disconnection to separate but colocalized fibre tracts in the subcortical parietal white matter. Contemporary neuroimaging techniques have correlated this syndrome with left posterior parietal lesions [7–9].

McCloskey et al. [10–12] and Caramazza and McCloskey [13] proposed a cognitive model regarding the processing of numbers and the relationship of arithmetical operations. This model includes a distinction between the processing system of numbers (an understanding mechanism and the production of numbers) in addition to the numerical calculation system that includes the necessary processing components to accomplish mathematical operations. In the event of brain injury, these components can be disassociated [14, 15].

Several classifications of acquired calculation disturbances are found in the literature (e.g., [16–19]). Luria [20],

for instance, distinguishes three different types of acalculia: optical acalculia, frontal acalculia, and primary acalculia. Hecaen et al. [18] also refer to three variants of acalculia: alexia and agraphia for numbers, spatial acalculia, and anarithmetia or primary acalculia. However, the most frequent distinction found in contemporary literature includes primary acalculia and secondary acalculias.

Ardila and Rosselli [16] proposed a comprehensive classification of acalculias. They distinguished six different types acalculia: (1) primary acalculia or anarithmetia, (2) aphasic acalculia, (3) alexic acalculia, (4) agraphic acalculia, (5) dysexecutive (frontal) acalculia, and finally (6) spatial acalculia. Primary acalculia corresponds to anarithmetia. The remaining types of acalculia are considered as secondary acalculias (Table 1).

A proposal for clinical intervention to rehabilitation of acquired acalculia is presented in this paper. It is important to emphasize that rehabilitation is based in both targeting restitution of the original impaired function and reorganization of functions employing other less or unimpaired cognitive functions [21, 22].

Table 1: Classification of acalculias (according to [16]).

Primary acalculia	Anarithmetia
Secondary acalculias	Aphasic acalculia
	In Broca aphasia
	In Wernicke's aphasia
	In conduction aphasia
	Alexic acalculia
	In central alexia
	In pure alexia
	Agraphic acalculia
	Dysexecutive (frontal) acalculia
	Spatial acalculia

2. Cognitive Rehabilitation of Acalculia

Research about acalculia rehabilitation has been limited [23]. Frequently, calculation disturbances are overlooked in cognitive assessments, and numerical ability is sometimes evaluated as a language-dependent ability. However, as in any rehabilitation procedure, the first step is clearly pinpointing the defect characteristics as well as defining the calculation abilities lost or maintained; for instance, sometimes patients with brain pathologies cannot perform arithmetical operations mentally, but they can do in writing; the opposite pattern can also be found. Furthermore, significant variables affecting calculation abilities, such as the education level and the patient's professional activity, must be taken into consideration. The types of errors should be recorded.

In a review of the research devoted to the rehabilitation of acalculia published from 1980 to 2007, only 7 papers were found, all of them single case studies [24]. Regardless of the positive results reported, it is difficult to know which procedure can be considered as the most effective technique in acalculia treatment due to the absence of group studies. For instance, in the Medline review, there were only three papers found reporting the treatment and evolution in acalculia covering the last ten years (2009-2019).

In one of the few studies analyzing the evolution of acalculia, Caporali et al. [25] reported 51 vascular acalculic patients examined at least twice. Results indicated that recovery from acalculia is frequently found during the first months poststroke; furthermore, the initial severity does not significantly influence recovery. Recovery correlates with recovery of auditory comprehension. In a more recent report, Basso et al. [26] examined the relationship between aphasia and acalculia in 98 left brain-damaged patients and the spontaneous recovery from acalculia in 92 acalculia patients. It was found that there is a significant association between aphasia and acalculia; however, 19 patients presented aphasia with no acalculia and six patients presented acalculia with no aphasia. A significant improvement was observed between a first examination carried out between 1 and 5 months postonset and a second examination carried out between 3 and 11 months later.

Few studies have analyzed the brain changes associated with acalculia recovery [27]. Claros-Salinas et al. [28] recorded fMRI in seven patients during calculation and perceptual tasks both before and after acalculia training. Regardless of the heterogeneity of brain lesions associated with acalculia, a common pattern of training-induced changes emerged. Performance improvements were associated with widespread deactivations in the prefrontal cortex. These deactivations were calculation-specific and only observed in patients exhibiting a considerable improvement after training. These findings suggest that the training-induced changes rely on an increase of frontal processing efficiency.

Major strategies used in the rehabilitation of primary and secondary acalculias will be presented. However, frequently cognitive rehabilitation procedures have been implemented in single cases; few studies have included large groups of acalculia patients.

3. Anarithmetia Rehabilitation

Primary acalculia is found associated with left posterior parietal lesions [29], usually including the intraparietal sulcus [30]. Tsvetkova [31] suggested that two deficits underlie primary acalculia: (1) an impairment in the spatial perception of numbers and in their mental representation and (2) a deficit in the verbal organization of this spatial perception. These patients present significant difficulties in spatial coordination systems, in other words, in understanding and internally representing spatial language [20, 31]. Several clinical manifestations are observed in cases of primary acalculia, including (1) defects in numerical concepts, (2) difficulties in the comprehension of the position of the numbers within the numerical continuum, for instance, understanding that 12 and 21 are different, (3) impairments in performing arithmetic sequences, for instance, adding or subtracting a certain quantity successively, such as 1, 4, and 7, and (4) defects in

arithmetic symbol understanding. Interestingly, these patients also have difficulties with tactile enumeration [32].

It has been observed that anarithmetia usually appears simultaneously with the so-called semantic aphasia [7, 20, 33, 34]; meaning, primary acalculia is associated with disturbances in understanding logical-grammatical relationships. Errors are observed in understanding comparative relations such as "greater than" or "less than," and therefore, patients cannot determine the magnitude relationship between numbers. For example, they may report that the number 97 is greater than the number 112, because they only consider the numerical value of each digit independently, ignoring the positional value. Regardless that the patients can read digits, their ability to conceptualize numbers is impaired. For example, they cannot recognize the number of dozens or hundreds within a number (e.g., 600) or understand that 30 is composed by $10 + 10 + 10$. Simply speaking, anarithmetia is characterized by the loss of understanding of how the numerical system is organized. Departing from this observation, it is easy to conclude that the fundamental aim in primary acalculia rehabilitation is recovering the understanding of numbers and their positional value within the numerical system; that is, numbers represent a quantity, but the quantity that they represent depends on their spatial location.

According to Tsvetkova [31], the initial step consists in organizing sets of elements (for instance, geometric figures) and relating them with a specific numerical value. To reinforce the understanding of quantities, other tasks can be introduced, such as dividing the objects into groups based on a particular feature of the objects, for example, their shape or color and counting the objects in each group while pointing to them. Later on, it is decided how many objects are in the set and writing the number on a paper. Once the acalculia patient has recovered the concept of digits and tens, the rehabilitation will target the concept of numerical composition as well as the relations between numbers; later, the idea of number manipulation through arithmetical operations (adding, subtracting) will be introduced. During this stage, the ordinal position of the numbers and their value depending on their location are explained to the patient and practiced. It is a good idea to initially use concrete elements, for instance, a potato chip, and progressively move to more abstract numerical representations.

Noteworthily, primary acalculia can be observed without language disturbances, but its correlation with aphasia is significant [26]. The rehabilitation of the calculation abilities can be implemented once a level of language understanding and production is acceptable. The recovery of aphasia evidently affects the recovery of calculation abilities. Caporali et al. [25] found that the spontaneous recovery of acalculia in patients with left vascular lesions correlated with the level of recovery in language comprehension.

In conclusion, rehabilitation of the patient with primary acalculia should begin by relearning the basic concepts of number. Later, the patient should move to the acquisition of more sophisticated concepts that imply the relationship between numbers and finally to solving arithmetical operations and numerical problems.

4. Secondary Acalculia Rehabilitation

4.1. Acalculia Associated with Language Defects. Patients with acalculia due to a language defect (aphasic acalculia) and receiving language therapy usually present a significant improvement in their calculation abilities in a parallel way to the language recovery [35]. In other words, the recovery of calculation disturbances in these patients is parallel to language rehabilitation program. Noteworthily, the calculation deficits are quite different in fluent and nonfluent forms of aphasia, but anyhow, the underlying deficit is the same: a defect in the syntax of the arithmetical operations in Broca's aphasia and a lexical understanding deficit in Wernicke's aphasia [16].

4.2. Acalculia Associated with Alexia and Visuoperceptual Defects. Sometimes brain-damaged patients can mentally solve mathematical operations, but they fail in recognizing numbers due to visuoperceptual impairments. The intervention in those cases should be directed to recover the visual perception [36]. Perceptual deficits will impair the performance of numerical tasks that require reading and/or writing. If the ability to write quantities is preserved as it is observed in cases of pure alexia—alexia without agraphia—making the movements as writing numbers in the air will help to its recognition. This same strategy is used to improve the ability to read words and is known as kinetic writing.

The technique known as "number reconstruction" [31] is based on the reconstruction of the number departing from some visual elements, for example, to finish writing numbers whose lines have already been started, such as completing the number 8 starting from number 3. Other strategies can also be used, such as looking for certain elements of a number in another number; for instance, to find the number 1 in the stroke of the number 4. Verbalizing the similarities and differences observed between the visual appearances of different numbers can also be helpful in the reconstruction of the numbers. Spatial orientation tasks, training of right-left dimensions, and analysis and identification of various geometric forms are exercises potentially contributing to the reconstruction of the number representations.

Patients with pure alexia—alexia without agraphia—have difficulties for the visual integration of stimuli (deficit that is known as simultanagnosia) and defects in visual-motor coordination (known as optic ataxia). Consequently, the intervention should include exercises that require the visual exploration of space. Frequently used tasks included in rehabilitation programs suppose a progressive increase in their level of difficulty, beginning with simple movements such as reaching objects, followed by tasks that require more complex movements such as copying figures in two dimensions to conclude with the copy of three-dimensional designs [37]. Training in the reproduction of designs of different shapes, colors, and sizes begin with help from a therapist. For example, a patient is asked to finish copying designs that are partially copied so that they progressively reproduce them completely independently [38].

When there is a visual exploration defect (ocular apraxia) impairing the ability to normally scan quantities, practicing eye-tracking exercises can help to overcome this defect. Rosselli et al. [36] described the rehabilitation of the reading and writing skills of a patient with Balint syndrome, presenting with severe ocular apraxia. Several exercises were used, including visual tracking of objects and working in dozens of trail making tests, specially designed for this patient. In other words, visuokinetic exercises were included in the rehabilitation program designed for this patient. Different letters were presented to him, and he had to reproduce in the air with his hand the movements required to write those letters.

4.3. Acalculia Associated with Executive Function Defects. Patients with frontal damage due to diverse conditions, such as head injuries and tumors, usually present executive function disturbances. These patients present particularly significant difficulties in solving mathematical problems. Written calculations are easier than mental calculations. Attentional difficulties significantly contribute to the calculation difficulties. Tsvetkova [31] suggested that providing these patients with attentional control strategies may result in a better attention control and reduction of perseverations. Attentional control strategies include the verbal descriptions of the sequence that is required to successfully solve an arithmetical problem. The patient can be trained to verbalize the operations required and follow them. This is a general procedure that is successfully used with patients with frontal damage and executive function disturbance: to verbalize, as a way to organize and control cognition.

4.4. Acalculia Associated with Spatial Defects. Spatial acalculia is usually observed in cases or right hemisphere damage associated with spatial neglect [39]. Spatial neglect refers to the inability to respond to the stimuli presented on the side contralateral to brain pathology (usually the left visual field) and represents a factor impairing the performance of written arithmetical operations. The ability to perform mental operations is much better preserved. Considering that patients with spatial neglect have difficulties to visually explore the surrounding space, several rehabilitation strategies have been proposed, including (1) placing a thick colored mark in the left margin of the sheet of paper and (2) numbering each line to be read. The patient is asked to find the colored mark before beginning to read; using the finger can help to the visual scanning. He has to initially find the numbers located at the beginning of each line. As the treatment advances, the verbal and visual cues are decreased up to the point that the patient is capable to read without the external support. The progressive decrease in neglect is clearly correlated with a decrease in spatial difficulties in reading words and numbers [40].

Rosselli and Ardila [41] described the rehabilitation treatment of a 58-year-old woman who presented alexia, agraphia, and spatial acalculia secondary to a right hemisphere vascular pathology. The rehabilitation program was based on the recovery of spatial neglect and associated spatial difficulties. Initially, the patient could normally perform oral arithmetic operations but was unable to make in written because of the spatial difficulties. In a written mathematical test including addition, subtraction, multiplication, and division, her score was 0/20. The left unilateral spatial neglect, the inadequate mix of procedures, and the impossibility to organize and follow the numbers inside the columns to add them up were very evident. After eight months of therapy, a significant recovery was observed and she was able to perform basic arithmetical operations in writing.

Benavides-Varela et al. [42] reported a large study including 30 right hemisphere-damaged patients and a controlled matched sample. The results showed that patients and controls significantly differ in number comprehension, transcoding, and written operations. Spatial errors were associated with extensive lesions in frontotemporoparietal regions, which frequently lead to neglect. Stepwise regression models consistently revealed that spatial errors were primarily predicted by composite measures of visuospatial attention/neglect and representational abilities. The authors suggest that unilateral right hemisphere lesions can directly affect core numerical/arithmetical processes and that right hemisphere acalculia is not only ascribable to visuospatial deficits as traditionally thought.

5. Conclusions

The available information about the cognitive rehabilitation of acquired calculation disturbances is limited. However, some general conclusions can be drawn.

(1) In primary acalculia, the fundamental therapeutic goal is to reconstruct the understanding of the numerical system. Patients with primary acalculia seemingly do not understand how the numerical system is organized

(2) In aphasic acalculia, numerical impairment and recovery in general parallelize aphasia impairment and recovery

(3) When acalculia is due to visuoperceptual disturbances, the fundamental aim of therapy is to recover visual perception

(4) In frontal dysexecutive acalculia, providing the patient with external support (e.g., writing) and attentional control strategies (e.g., verbalizing) may result in improving the numerical defect

(5) Neglect represents probably not the only but the fundamental defect responsible for the written calculation defects observed in patients with right hemisphere damage. Some simple strategies, such as using clear marks to indicate where to begin to read, can successfully improve the calculation defects

Conflicts of Interest

No conflict of interests exists in this paper.

References

[1] A. Ardila, "Acalculia," *Medlink: Neurology*, 2018.

[2] B. Butterworth, "Developmental dyscalculia," in *Child Neuropsychology: Concepts, Theory and Practice. Chichester*, J. Reed and J. Warner-Rogers, Eds., Wiley-Blackwell, UK, 2008.

[3] S. E. Henschen, "Clinical and anatomical contributions on brain pathology," *Archives of Neurology and Psychiatry*, vol. 13, no. 2, pp. 226–249, 1925.

[4] H. Berger, "Über rechenstörungen bei herderkrankungen des großhirns," *Archiv für Psychiatrie und Nervenkrankheiten*, vol. 78, no. 1, pp. 238–263, 1926.

[5] J. Gerstmann, "Syndrome of finger agnosia, disorientation for right and left, agraphia and acalculia," *Archives of Neurology & Psychiatry*, vol. 44, no. 2, pp. 398–408, 1940.

[6] E. Rusconi, P. Pinel, S. Dehaene, and A. Kleinschmidt, "The enigma of Gerstmann's syndrome revisited: a telling tale of the vicissitudes of neuropsychology," *Brain*, vol. 133, no. 2, pp. 320–332, 2010.

[7] A. Ardila, "A proposed reinterpretation of Gerstmann's syndrome," *Archives of Clinical Neuropsychology*, vol. 29, no. 8, pp. 828–833, 2014.

[8] A. Ardila, M. Concha, and M. Rosselli, "Angular gyrus syndrome revisited: acalculia, finger agnosia, right-left disorientation and semantic aphasia," *Aphasiology*, vol. 14, no. 7, pp. 743–754, 2000.

[9] A. Ardila and M. Rosselli, "Acalculias," *Behavioural Neurology*, vol. 3, 48 pages, 1990.

[10] M. McCloskey, A. Caramazza, and A. Basili, "Cognitive mechanisms in number processing and calculation: evidence from dyscalculia," *Brain and Cognition*, vol. 4, no. 2, pp. 171–196, 1985.

[11] M. McCloskey, S. M. Sokol, and R. A. Goodman, "Cognitive processes in verbal number processing: inference from the performance of brain-damaged subjects," *Journal of Experimental Psychology: General*, vol. 115, pp. 313–330, 1986.

[12] M. McCloskey, D. Aliminosa, and P. Macaruso, "Theory based assessment of acquired dyscalculia," *Brain and Cognition*, vol. 17, no. 2, pp. 285–308, 1991.

[13] A. Caramazza and M. McCloskey, "Dissociation in calculation processes," in *Mathematic Disabilities: A Cognitive Neuropsychological Perspective*, G. Deloche and X. Seron, Eds., pp. 221–234, Erlbaum, Hillsdale, NJ, USA, 1987.

[14] D. Dagenbach and M. McCloskey, "The organization of arithmetic facts in memory: evidence from a brain-damaged patient," *Brain and Cognition*, vol. 20, no. 2, pp. 345–366, 1992.

[15] M. Pesenti, X. Seron, and M. Van Der Lider, "Selective impairment as evidence for mental organisation of arithmetical facts: BB, a case of preserved subtraction?," *Cortex*, vol. 30, no. 4, pp. 661–671, 1994.

[16] A. Ardila and M. Rosselli, "Acalculia and dyscalculia," *Neuropsychology Review*, vol. 12, no. 4, pp. 179–231, 2002.

[17] J. Grafman, "Acalculia," in *Handbook of Neuropsychology (Vol. 1)*, F. Boller, J. Grafman, G. Rizzolatti, and H. Goodglas, Eds., Elsevier, Amsterdam, 1988.

[18] H. Hecaen, T. A ngelergues, and S. Houiller, "Les varietes cliniquesdes acalculies au cours des lesions retrorolandiques," *Revue de Neurologie*, vol. 105, pp. 85–103, 1961.

[19] H. Levin, F. C. Goldstein, and P. A. Spiers, "Acalculia," in *Clinical Neuropsychology*, K. M. Heilman and E. Valenstein, Eds., Oxford University Press, New York, NY, USA, 3rd edition, 1993.

[20] A. R. Luria, *Las Funciones Corticales Superiores en el Hombre*, Editorial Orbe, La Habana, 1977.

[21] K. Willmes, "Acalculia," in *Handbook of Clinical Neurology, Vol 88 (3rd Series) Neuropsychology and Behavioral Neurology*, G. Goldenberg and B. L. Miller, Eds., pp. 339–358, Elsevier, Amsterdam, 2008.

[22] L. Zaunmüller, F. Domahs, K. Dressel et al., "Rehabilitation of arithmetic fact retrieval via extensive practice: a combined fMRI and behavioural case-study," *Neuropsychological Rehabilitation*, vol. 19, no. 3, pp. 422–443, 2009.

[23] M. Cappelletti and L. Cipolotti, *The Neuropsychological Assessment and Treatment of Calculation Disorders*, Oxford University Press, 2010.

[24] A. Basso, S. Cattaneo, L. Girelli et al., "Treatment efficacy of language and calculation disorders and speech apraxia: a review of the literature," *European Journal of Physical and Rehabilitation Medicine*, vol. 47, no. 1, pp. 101–121, 2011.

[25] A. Caporali, F. Burgio, and A. Basso, "The natural course of acalculia in left-brain-damaged patients," *Neurological Sciences*, vol. 21, no. 3, pp. 143–149, 2000.

[26] A. Basso, A. Caporali, and P. Faglioni, "Spontaneous recovery from acalculia," *Journal of the International Neuropsychological Society*, vol. 11, no. 1, pp. 99–107, 2005.

[27] B. Bernal, A. Ardila, and N. R. Altman, "Acalculia: an fMRI study with implications with respect to brain plasticity," *International Journal of Neuroscience*, vol. 113, no. 11, pp. 1505–1523, 2003.

[28] D. Claros-Salinas, G. Greitemann, T. Hassa et al., "Neural correlates of training-induced improvements of calculation skills in patients with brain lesions," *Restorative Neurology and Neuroscience*, vol. 32, no. 4, pp. 463–472, 2014.

[29] M. Grimaldi and R. Jeanmonod, "Acute stroke presenting with isolated acalculia," *The American Journal of Emergency Medicine*, vol. 36, no. 10, pp. 1923.e1–1923.e3, 2018.

[30] S. Dehaene, N. Molko, L. Cohen, and A. J. Wilson, "Arithmetic and the brain," *Current Opinion in Neurobiology*, vol. 14, no. 2, pp. 218–224, 2004.

[31] L. S. Tsvetkova, "Acalculia: aproximación neuropsicológica al análisis de la alteración y la rehabilitación del cálculo," in *Rehabilitación neuropsicológica*, F. Ostrosky, A. Ardila, and R. Dochy, Eds., Trillas, México, 1996.

[32] Z. Z. Cohen, I. Arend, K. Yuen et al., "Tactile enumeration: a case study of acalculia," *Brain and Cognition*, vol. 127, pp. 60–71, 2018.

[33] A. Ardila, "On the origins of calculation abilities," *Behavioural Neurology*, vol. 6, no. 2, 97 pages, 1993.

[34] A. Ardila, M. V. López, and E. Solano, "Semantic aphasia reconsidered," in *Brain Organization of Language and Cognitive Processes*, A. Ardila and F. Ostrosky-Solis, Eds., Plenum Press, New York, NY, USA, 1989.

[35] A. Basso, *Aphasia and Its Therapy*, Oxford University Press, 2003.

[36] M. Rosselli, A. Ardila, and C. Beltran, "Rehabilitation of Balint's syndrome: a single case report," *Applied Neuropsychology*, vol. 8, no. 4, pp. 242–247, 2001.

[37] M. M. Sohlberg and C. A. Mateer, *Cognitive Rehabilitation: An Integrative Neuropsychological Approach*, Guilford Publications, 2017.

[38] Y. Ben-Yishay, *Working Approaches to the Remediation of Cognitive Deficits in Brain Damaged Persons. Rehabilitation Monographs*, NYU Medical Center Institute of Rehabilitation Medicine, New York, NY, USA, 1983.

[39] A. Ardila and M. Rosselli, "Spatial acalculia," *International Journal of Neuroscience*, vol. 78, no. 3-4, pp. 177–184, 1994.

[40] A. Ardila and M. Rosselli, *Neuropsicologia Clinica*, Manual Moderno, México, 2007.

[41] M. Rosselli and A. Ardila, "Rehabilitación de la alexia y la agrafía," in *Rehabilitación neuropsicológica*, F. Ostrosky, A. Ardila, and R. Dochy, Eds., Trillas, México, 1996.

[42] S. Benavides-Varela, D. Piva, F. Burgio et al., "Re-assessing acalculia: distinguishing spatial and purely arithmetical deficits in right-hemisphere damaged patients," *Cortex*, vol. 88, pp. 151–164, 2017.