

■ Go/NoGo training improves executive functions in an 8-year-old child born preterm

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Abstract

The Go/NoGo paradigm is the most important tool for the assessment of inhibitory control. However, it has not been implemented as a training source consistently. Inhibitory control has been proposed as a key process at the basis of multitude of superior cognitive functions. We propose that the training Go/NoGo paradigm is a simple, fast and easy-to-program and that it will conduce to significant improvements in most of the executive functions. An 8-year-old male child born preterm and with clear signs of inhibitory control dysfunction was trained with a visual Go/NoGo Task for 7 consecutive days (\approx 4 minutes per day). Sustained, alternating and divided attention, cognitive flexibility, visuo-spatial capacity and inhibitory control were assessed with standardized neuropsychological tests for the Spanish population. Improvements in inhibition and other superior cognitive functions were observed. This is the first time that short-term training with a Go/NoGo Task has been linked to significant improvements in the human superior cognitive functions. This data reinforces previous knowledge which points out that inhibitory control plays a key role in the maintenance of the rest of executive functions, and it demonstrates that such functions can be improved at clinical levels by low-cost and easy to develop informatics systems.

Keywords: executive functions, inhibition, ICT-based Go/NoGo Task, preterm birth, single-case experiment.

Abstract

El entrenamiento mediante tarea Go/NoGo mejora las funciones ejecutivas en un niños de 8 años nacido pretérmino. El paradigma Go/NoGo es ampliamente usado para evaluar el control inhibitorio. Sin embargo, no ha sido implementado consistentemente como un recurso de entrenamiento. El control inhibitorio ha sido propuesto como clave para el mantenimiento del resto de las funciones cognitivas. Propusimos que un entrenamiento corto mediante una tarea Go/NoGo simple y fácil de diseñar producirá mejoras significativas en la mayor parte de las funciones ejecutivas evaluadas. Se entrenó mediante una tarea Go/NoGo visual durante 7 días a un niño varón pretérmino de 8 años y con un control inhibitorio alterado. Se evaluaron atención sostenida, alternante y dividida, flexibilidad cognitiva, capacidad visuo-espacial y control inhibitorio mediante pruebas neuropsicológicas estandarizadas para población española. Se observaron mejoras importantes tanto en inhibición como en el resto de las funciones cognitivas evaluadas. Esta es la primera vez que un entrenamiento de tan corto tiempo con una tarea Go/NoGo se relaciona con mejoras significativas en funciones humanas superiores. Este tipo de resultados refuerza el conocimiento actual de que el control inhibitorio juega un rol central en el mantenimiento del resto de funciones ejecutivas y demuestra que dichas funciones se pueden mejorar a nivel clínico con sistemas informáticos de bajo coste y de fácil desarrollo.

Palabras clave: funciones ejecutivas, inhibición, tarea Go/NoGo formato TIC, nacimiento pretérmino, experimento de caso único.

Over the last few decades, many studies have demonstrated that children born preterm (< 32-37 weeks' gestation) and with very low birth weight [VLBW <1,500 g (Voigt, Pietz, Pauen, Kliegel, & Reuner, 2012)], represent a potential risk group for the early development of cognitive alterations, showing deficits in memory (Aanes, Bjuland, Skranes, & Løhaugen, 2015), attention (Giordano et al., 2014; van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008), and executive functions (Burnett, Scratch, & Anderson, 2013).

One of the most relevant features of executive functions is the

inhibitory control. This is defined by the capacity to control cognition by blocking out irrelevant stimuli (Diamond, 2005), being under control of fronto-striatal brain networks (Aron et al., 2007; Aron, Poldrack, & Robbins, 2004). The study of inhibitory control deficits in individuals born preterm has tried to consider different birth times or characteristics for its analyses; by focusing on preterm with intrauterine growth restriction (Réveillon et al., 2013), late preterm birth - 34-36 weeks' gestation (Brumbaugh, Hodel, & Thomas, 2014)], very preterm birth [\leq 30 weeks' gestation (Aarnoudse-Moens, Smidts, Oosterlaan, Dui-

envoorden, & Weisglas-Kuperus, 2009)], extremely preterm birth [\leq 25 weeks' gestation (Marlow, Hennessy, Bracewell, Wolke, & Group, 2007)], children born preterm with/without cerebral injuries (Katz et al., 1996) and children born preterm with VLBW (Böhm, Smedler, & Forssberg, 2004), amongst others. All these studies showed impaired inhibitory control in the whole range of preterm criteria.

Studies on the capacity to inhibit improper behaviors point to the existence of, at least, two different types of impulsivity (Luengo, Carrillo de la Peña, & Otero, 1997). On the one hand, a motor type, this defines the participant's capacity to inhibit prepotent unsuitable responses. On the other hand, a cognitive type, this represents the capacity to self-orientate forward to the future and to wait for the reinforcement. Both types are related to cognitive flexibility (capacity to intermittently change the focus of attention), inhibitory control, and working memory (Etchepareborda & Mulas, 2004), showing the importance of proper inhibition in order to suitably maintain the rest of the executive functions.

The Go/NoGo paradigm is one of the main Information and Communication Technologies (ICT) based tasks designed for the evaluation of inhibitory control and response control in clinical and applied neuropsychology (Casey et al., 1997). This ICT task consists of the presentation of one stimulus, which encourages the participant to respond (Go). At the same time, a non-responding associated stimulus is also displayed (NoGo), forcing the participant to withhold the response. The Go stimulus is displayed a greater number of times in order to bring about a prepotent response. This paradigm has been extendedly used for the assessment of inhibitory control in patients with psychiatric disorders (Welander-Vatn et al., 2013), delinquents (Guan et al., 2015), drugs abusers (Nicholls, Bruno & Matthews, 2015; Pandey et al., 2015), and children born preterm (Réveillon et al., 2013; Aarnoudse-Moens et al., 2009).

However, the use of the Go/NoGo paradigm as an ICT based, inhibitory control training procedure has not been significantly explored further altered consumption behavior, with single-session and very short-term effects assessment (for studying in depth, see Jones et al., 2016). The majority of studies have been focused on practice effects and its correlation to physiological differences between Go and NoGo stimuli responses. In particular, an early study conducted by Jodo & Inoue (1990) demonstrated that, after 6 days of training with a Go/NoGo Task (200 trials/day), neurophysiological outcomes in No/Go P300 changed by reducing its latency, demonstrating that Go-P300 and NoGo-P300 are separate event-related potential (ERP) components.

Taking in account the widespread success of the Go/NoGo paradigm and its variants in the assessment of inhibitory control (Casey et al., 1997; Moreno et al., 2012; Smith, Johnstone & Barry, 2004), including impulsive behavior in children born preterm (Aarnoudse-Moens et al., 2009; Réveillon et al., 2013), and the significant neurophysiological (and, to a lesser degree, behavioral) differences, the main objective of the present research was to study whether this ICT task could be used as a rehabilitation tool. Thus, we used the Go/NoGo paradigm with the aim of train and improve attention and executive dysfunctions further to inhibitory control, widely altered in children born preterm. For that purpose, we present here a single-case study of one child born preterm and with VLBW, with clear signs of restlessness and impatience. We analyze whether 7 days of intervention with a visual Go/NoGo task can lead to a general improvement of the performance in standardized neuropsychological tests. We hypothesize that this training program could improve cognitive functions related to executive and attentional performance.

Case description

This study was conducted following the World Medical Assembly Declaration about the Ethical Principles for Medical Research Involving Humans in Helsinki (1964), and it was approved by the bioethics committee for human research from the University of Almería.

Patient's identification

The experimental participant was one male, 8 years old at the moment of the training. He was born by controlled multiple pregnancy, and a cesarean birth at Week of gestation was conducted. He was born with very low weight at birth was (1400-g) and was identified as VLBW preterm child. He has presented normalized development, with good relations with friends and family. He has grown up in a medium- to high-class family.

Reason for consultation and history of the problem

Altered attentional performance and hyper activated behavior have been reported in the last 2 years, mainly by his parents and teachers as well as friends and family. Despite of the fact that he is still getting notable marks in his studies (primary elementary school), such behaviors are deteriorating his relationships. He has received any treatment (nor psychological neither pharmacological) for such behaviors beyond this experimental protocol.

Evaluation of the case

General neuropsychological screening

The evaluation was carried out by a specialist in clinical neuropsychology. An initial interview with the parents, evaluation protocol with standardized neuropsychological tests and semi-structured observation were included. It was carried out in a single clinical session of 45 minutes and it was geared towards the evaluation of the state of the main cognitive functions, above all attention and executive performance. Training with a simple visual Go/NoGo Task was conducted for 7 consecutive days. Before starting the training procedure, specific neuropsychological tests were used for baseline (BL) performance in order to evaluate different cognitive functions. Once the training finished, such neuropsychological tests were implemented in order to evaluate possible training effects (Post training performance, with parallel task versions).

Specific neuropsychological tests. BL and Post training evaluations were conducted with standardized tests for Spanish population: Subtests Trail (grey and in color) and Interference were used (from the "Neuropsychological evaluation of executive functions in children" battery (EFEN, Portellano, Martínez, & Zumárraga, 2009), as well as the Spanish version of the CARAS-R perception of differences test, (Thurstone & Yela, 2012). Parallel versions of each test were done in order to avoid learning effects.

Grey and in color Trail tasks. In grey Trail task (Part A), the participant has to link the different numbers (from 20 to 1) in a descending order as fast as possible. These numbers are distributed randomly over a piece of paper. Conversely, in color trail task (Part B), the participant has to link the numbers (from 1 to 21) in an ascending order, alternating between those printed in pink, and those in yellow. Both tasks give us two different scores (one for Part A and one for Part B), as it is an equivalent task to the Trail Making Test Part A/B. Data recorded in both Parts are: Total time required to complete the sequence, omis-

sion errors (numbers which are not linked) and substitution errors (incorrect numbers linked). Final performance is calculated by subtracting the total number of mistakes from the total number of correct responses. This task assesses sustained and alternating attention, cognitive flexibility and visuo-spatial capacities.

Interference subtest. The Interference Subtest is defined by 39 printed words on a sheet with names in color (blue, green, yellow and red). They are written in an ink color completely different from the one expressed by its semantic meaning (i.e. the word “red” is printed in blue ink). The words are displayed in three different vertical columns with 13 words per column. The participant has to state the color, not the word. Performance is recorded by the total time that the participant needs to complete the whole task. At the same time, total number of errors by omission (unmentioned colors) and errors by substitution (incorrect color stated) are recorded. Each correct answer and error is given a value of 1 point. Final performance data is calculated by subtracting the total number of mistakes from the total number of correct responses. This task is equivalent to the Stroop task, and it assesses attentional and inhibitory control.

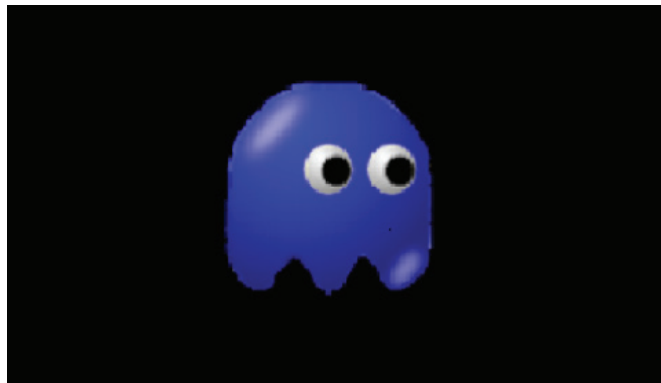
Differences perception Test (CARAS-R). The Differences perception Test (CARAS-R) is composed of 60 graphic elements, which symbolize drawings of faces, with their constituent elements (i.e. mouth, eyes, brows, hair, etc.). The aim of the test is to identify which face is different amongst the 3 options and to strike it out. Three minutes is allowed in order to complete the task, and total correct responses are recorded. It mainly assesses sustained and selective attention.

Treatment application (Go/NoGo task as an ICT rehabilitation source)

An adapted computer-based visual Go/NoGo task (Neutral stimuli) for children in the ePrime application suite 2.0.10.356 (Psychology software tools, Inc) was used. This protocol was conducted for 7 sessions (once per day, 7 consecutive days). We included three important changes in our procedure: 1) We focus on general impulsive outcomes, 2) Neutral stimuli were always displayed in order to discard emotional influences, 3) Repetitive training was proposed. Added to this, we focused on the effects of inhibitory control training on high-order cognitive functions.

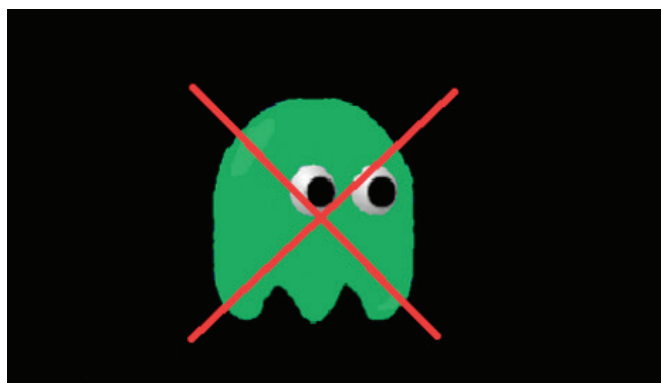
Go stimulus (participant has to respond by pressing the space bar) was associated with a blue ghost, and NoGo stimulus (participant has to withhold the response) was associated with a green ghost (Figures 1 and 2). The participant was informed to respond as quickly and accurately as he could. In order to force prepotent behavior, Go stimulus was displayed 75% of the time, while NoGo stimulus made up the other 25% (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). Dependent variables were as follows: Errors by commission (responding when NoGo stimulus is displayed), errors by omission (non-responding when Go stimulus is displayed) and reaction time (RT) for each Go stimulus. The total display time for each stimulus was set at 400ms in the center of the screen (fixed reaction time deadline). Each stimulus presentation was always preceded by a fixation point in the center of the screen for 500ms. Between each stimulus presentation and the next fixation display, 500ms of black background (the same color as the background during stimulus and fixation point presentation) was introduced. This comprised a total of 1000ms of inter-stimulus interval. The total number of trials was 168 per sessions, with 8 initial practice trials. Randomized distribution was programmed. Less than 4 minutes were needed in order to complete the daily training. A total of \approx 28 minutes of training were conducted for the whole experiment.

Figure 1. Example Go stimulus.



Patient must to press space bar for correct response.

Figure 2. Example NoGo stimulus.



Patient must avoid pressing space bar for correct non-response. The red cross is added to indicate the order of no respond; such cross was not displayed on original procedure.

Data analysis

A single-case study design was used for the present experiment. Visual analysis session-by-session qualitative analysis was conducted for every single behavior: RTs were analyzed in the Trail Task (both A/B), and in the Interference Task. Total correct responses were analyzed in the CARAS-R Task. In the Go/NoGo Task, omissions, commissions, total accuracy and RTs were recorded in every single session. Figures were designed with GraphPad Prism v6.05.

Results

Development of Performance in Go/NoGo

Development of omissions (Go) and commissions (NoGo)

The BL session (first day of training) showed a higher number of omissions (BL= 58) compared to the rest of training sessions, being successively reduced in each training session till the last one (S6 = 24, improvement of 58.62%). Moreover, a reduction of commission errors was also observed at S1, S2 and S3 compared to BL session, but at session S4 and S5 there were a worst performance, which was reversed at session S6 by returning to BL levels (Figure 3).

Development of total correct responses and total accuracy percentage

Both the total correct responses in Go stimuli and total accu-

racy percentage showed a manifest improvement represented by an ascending progression, with a peak performance in the last session for both (TotalAcc from BL = 57.5% to S6 = 78.8%, improvement of 21.3%; AccGo from BL= 51.7% to S6 = 80%, improvement of 28.3%) (Figure 4). Meanwhile, accuracy in NoGo showed the widest variability, but a clear ceiling effect was observed throughout the whole training period (AccNoGo from BL= 75% to S6 = 75%).

Figure 3. Evolution of total number of omissions and commissions through 7 training sessions.

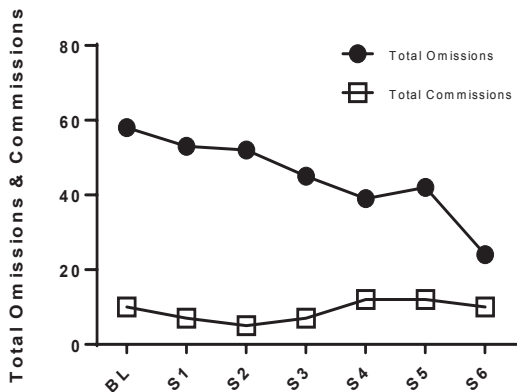


Figure 4. Percentage for correct responses when Go (black circle), NoGo (white square) and percent accuracy (grey triangle) both stimuli were displayed through 7 training sessions.

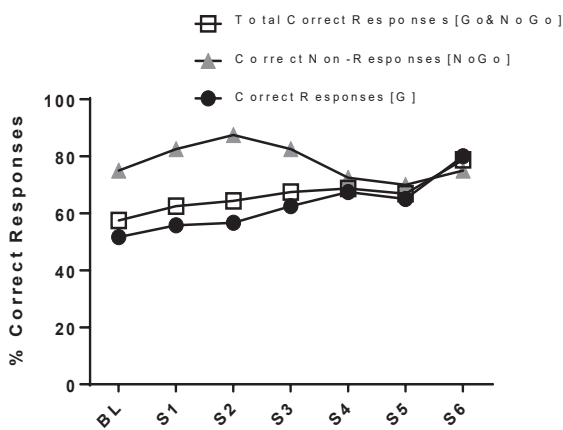
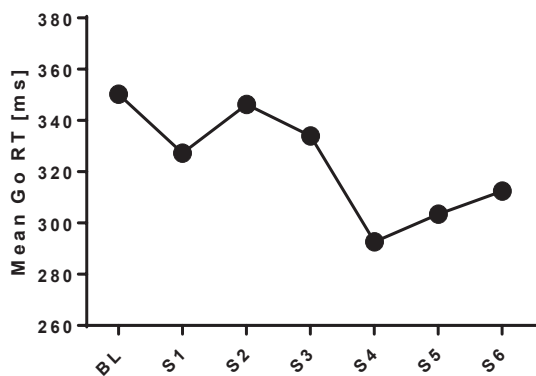


Figure 5. Mean Reaction Time when Go Stimulus was displayed through 7 days of training.



Development of RTs

Figure 3 shows the participant’s RTs development per session. It demonstrates a clear progression in the reduction of the mean time response when the Go stimulus was present throughout the experiment. Thus, the participant’s mean RT changed from 350.26ms at baseline to 312.49ms (improvement of 10.78%) on the final training day (S6), with a peak performance of 292.69ms in S5 (improvement of 16.44%) (Figure 5)

Comparisons in Pre-Post Training: Neuropsychological Tests

After 7 consecutive days of training with a Go/NoGo Task, the participant did not improve performance in Trail A (From BL = 69s to Post = 77s). Nevertheless, a large training effect was observed in performance in Part B (from BL= 185s to Post= 113s, improvement of 38.92%). Total time taken by the participant to complete the Interference Task was reduced after training (from BL = 72s to Post = 59s, improvement of 18.06%) (Table 1). Finally, the participant’s performance in the CARAS-R task improved after training (from BL= 23 correct responses to Post = 28 correct responses, improvement of 21.74%).

Table 1. Baseline and PostTraining Data of standardized neuropsychological Tasks.

Test	Baseline Data			PostTraining Data		
	Time	Decatype	Performance	Time	Decatype	Performance
TrailTask A	69s	8	High	77s	7	Med-High
TrailTask B	185s	5	Medium	113s**	8	High
Interference	72s	5	Medium	59s*	6	Medium
CARAS-R	Correct Responses: 23			Correct Responses: 28*		

Time (Seconds) Decatype [Level of difficulty (quantitative)], Performance [Level of difficulty (qualitative)], and Correct Responses (Number of Correct Responses). * and ** refer to significant (qualitatively) and very significant improvements from baseline performance, respectively.

Discussion

The present study shows an improvement in high-order executive functions in an 8-year-old child born preterm and with VLBW through a brief training (~4 minutes per day) of inhibitory control performance for 7 consecutive days with a ICT computer-based visual Go/NoGo Task. The improvement in high-order executive functions was assessed by the changes in sustained attention, attention alternation, cognitive flexibility and attentional control evaluated with standardized neuropsychological test commonly used for clinical approaches, before and after the training in the Go/NoGo task. This is, to our knowledge, the first time that this simple paradigm has been used as a treatment choice, beyond its well-known assessment use, and its positive effects on superior cognitive functions are very widespread.

With an emphasis on executive functions, inhibitory control has recently been studied in children born preterm, as they are the most widely affected (Aarnoudse-Moens et al., 2009; Brumbaugh, Hodel, & Thomas, 2014; Böhm, et al., 2004; Katz et al., 1996; Marlow et al., 2007; Réveillon et al., 2013). Indeed, the Go/NoGo Task is one of the most developed paradigms for the evaluation of inhibitory control, and its repetitive practice has shown both neurophysiological and behavioral changes in inhibitory control (Jodo & Inoue 1990; Benikos et al., 2013). As an alternative, we proposed that, due to

its characteristics, this paradigm could be used as a treatment in neurorehabilitation programs for impulsivity, and we hypothesized that this training could even go further, improving executive and attentional functions, closely-related with inhibitory control. We considered this option for an 8 year old male child with clear signs of motor and cognitive impulsivity, over a period of 7 consecutive days (≈ 4 minutes/day). Such ICT format was chosen due to the large advantages respecting traditional paper-based ones (more reliable data, increased motivation for the patient, faster application and more controlled strange variables due to its immersive features).

Following on from this, the development in the participant's performance in the Go/NoGo Task showed a normalized learning curve, the total number of omissions was reduced in the training sessions, compared with the baseline data. Nevertheless, commissions' errors showed a clear floor effect from the beginning. This phenomena is coherent with the Task's design, where the stimuli centralization could lead to conservative behavior (few responses), with initial high levels of omissions and low rates of commissions, where sustained and divided attention conservation are essential for a proper performance. At this level, the reduction in the omission errors demonstrates an improvement in the task performance by training, with improved attention processes, without conducting to impulse responses, because NoGo performance was not impoverished.

The Go stimulus RTs showed significant improvements by task training over time, indicating a clear learning effect, with enhancements in process capability, order, and with a more precise, faster motor action. These results support previous behavioral improvement data after a short (7 days) Go/NoGo Task practice, as carried out by Benikos et al. (2012), unlike others works, which only demonstrated physiological modulations (Nakata, Sakamoto & Kakigi, 2015).

The inhibitory control improvement by training in the Go/NoGo Task has also shown to be generalized when comparing the pre and post measures in standardized neuropsychological tests. The participant showed great improvement in Trail subtest (Part B), by reducing the mean of total time required for its finalization. This result indicates an important development in cognitive functions such as: motor abilities, visuo-spatial function, sustained attention, cognitive flexibility and divided attention. The participant's performance in the Interference Test after treatment with a Go/NoGo Task showed an improvement in executive attentional control and inhibitory control, something observed in the improvement in the Go/NoGo Task. Finally, the CARAS-R Test demonstrated that the mean of identifications was improved after treatment with the Go/NoGo Task, which indicates an improvement in sustained and divided attention.

All these changes in a wide range of executive functions after selective training in inhibitory control and attention are not surprising. Inhibitory control is known to have a key role on many other cognitive functions, especially at a higher-order, as is the case of attention (Hester et al., 2004), working memory (Roncadin, Pascual-Leone, Rich & Dennis, 2006), action monitoring (Cooper & Shallice, 2000) and task switching (Monsell, 2003), all simple processes needed in order to maintain the rest of the cognitive functions. Furthermore, this demonstrates that simple computer-based programs can lead to interesting improvements in those complex functions in children born preterm. Thus, our visual Go/NoGo represents a common, easy to program and apply paradigm which could be proposed as a treatment/training system beyond preterm children. The capacity to exercise control over inhibition and sustained attention is essential due to the fact that they are key elements in many pathologies regarding the development of cognitive alterations as attention deficit/hyperac-

tivity disorder (Smith, et al., 2004, Huntington's disease (Beste, Saft, Andrich, Gold, & Falkenstein, 2008), and drug consumption (Charles-Walsh, Furlong, Munro, & Hester, 2014; Moreno et al., 2012).

Nevertheless, there are two main limitations in the present study: (1) the difficulty to compare our data with previously carried out research and (2) the sample size. Due to the novelty of this study, it is very difficult for us to compare our results to previously carried out procedures. It is the first time that this paradigm has been used as a treatment choice for the improvement of different cognitive functions. A recent Norwegian study, conducted by Grunewaldt, Løhaugen, Austeng, Brubakk, and Skranes (2013), demonstrated how simple computer-based working memory (WM) training can lead to a general improvement in the cognitive function of children born preterm and with VLBW. These results support previous reports that proposed the specific training of WM as a good approach for general cognitive improvement (Chein & Morrison, 2010; McNab et al., 2009). These studies are, as we demonstrate here, a clear proof of the power of specific training of key executive functions in order to facilitate general improvement for the whole range of cognitive functions.

The sample size is a clear limitation in the present study. Being a single-case study, the development of new research, in which children born preterm and with VLBW will undergo a Go/NoGo Task training protocol, is needed in order to ensure that this simple and easy to design approach is a good choice for the treatment of impulsiveness. Also, comparisons in performance and development with children born at term would be desirable. The benefits of this training could be generalized to other pathological collectives whose inhibitory control is altered, in order to study the influence of its modulation over different executive functions. Finally, this study must to be added to the large amount of studies that demonstrated the utility of ICT-based sources, both for rehabilitation and assessment, on different cognitive functions.

Conflict of interest

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

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