Article

Effects of Neurofeedback in the Working Memory of Children with Learning Disorders: An EEG Power-Spectrum Analysis

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Abstract: Learning disorders (LD) are diagnosed in children impaired in the academic skills of reading, writing and/or mathematics. Children with LD usually show a slower resting-state electroencephalogram (EEG), with EEG patterns corresponding to a neurodevelopmental lag. LD-children also show a consistent cognitive impairment in working memory (WM), including an abnormal task-related EEG with an overall slower EEG activity of more delta and theta power, and less gamma activity in posterior sites; task-related EEG patterns considered indices of an inefficient neural resource management. Neurofeedback (NFB) treatments aimed at normalizing the resting-state EEG of LD-children have shown improvements in cognitive-behavioral indices and diminished EEG abnormalities. Given the typical findings of a WM impairment in LD-children; we aimed to explore the effects of a NFB treatment in the WM of children with LD, by analyzing the WM-related EEG power-spectrum. We recruited 18 children with LD (8-10 years old). They performed a Sternberg-type WM-task synchronized with an EEG of 19 leads (10-20 system) twice in pre-post treatment conditions. They went through either 30 sessions of a NFB treatment (NFB-group, n= 10); or through 30 sessions of a placebo-sham treatment (Sham-group, n= 8). We analyzed the before-after treatment group differences for the behavioral performance and the WM-related power-spectrum. The NFB group showed faster response times in the WM-task post-treatment. They also showed an increased gamma power at posterior sites and a decreased beta power. We explain these findings in terms of NFB improving the maintenance of memory representations coupled with a reduction of anxiety.

Keywords: Neurofeedback; Learning Disorders; Working Memory; School-age Children; EEG Power Spectrum; Source Localization

1. Introduction

A Learning disorder (LD) is a neurodevelopmental impairment with a prevalence of 5-20% in children and adolescents between 5 to 16 years old [1–4]. A child diagnosed as a specific LD has significant difficulties in learning the academic skills of reading, writing, or mathematics, with these skills being remarkably lagged for his/her age and schooling [2]. A child with LD having a combined deficiency in two or three of these skills belongs to a subtype of LD, formerly known as LD not otherwise specified [5]. The co-occurrence of academic impairments appears in up to 80% of the LD cases [6]; and a specific learning disorder of reading is the most commonly found LD subtype, appearing alone or in combination with the other two specific disorders (writing or mathematics) in 4 out of 5 cases of LD [2].

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Coupled with the lagged academic skills, children with LD usually endure a heterogenous frame of cognitive impairments in processes such as phonological awareness, attentional control, processing speed, and working memory (WM) [6], the latter process being a main source of this heterogeneity [7]. WM is the part of memory in charge of the online processing of information in a type of limited-capacity mental workspace to achieve goal-directed actions [8]. This process is a commonly affected cognitive domain in LD children [9–11], being an adequate predictor of current and future academic difficulties [12, 13]. The WM performance is more severely affected in LD with co-occurrence of other academic impairments [6]. A defective WM implies a diminished capacity for the access, maintenance, and/or retrieval of information, usually of a phonological nature. It is relevant to highlight that school-age children require adequate WM functioning to properly develop their basic academic skills [12, 14]. Children with LD are also at an increased risk to suffer emotional disturbances in dealing with school issues [15, 16]. An affective distress in LD often appears in the form of reduced self-esteem coupled with possible anxiety and depression problems that can aggravate further into adolescence and adulthood [17].

The neural correlates of a child with LD have been identified with quantitative electroencephalogram (EEG) analyses of a resting-state [18]. The resting-state EEG of LD children usually shows an abnormally slower EEG activity than age-matched children with typical development. The slower EEG activity of children with LD is akin to that of younger healthy children, with more theta power in frontal regions and less alpha power in posterior (parietal and occipital) regions. This apparent lag in the brain functional development of LD children has led to the hypothesis of LD as a developmental disorder with a delay in the EEG maturation that impairs the abilities to keep up with a given grade at school [19–21].

The task-related EEG, recorded during the performance of WM tasks, has been examined with main techniques such as event-related potentials (ERP) and power-spectrum analyses. The Sternberg WM task [22] has been used because it allows a proper isolation of the different WM phases: encoding, maintenance, and retrieval. In an ERP study of poor readers *vs.* normal control children who responded to a Sternberg WM task, it was found that poor-readers had longer and larger P300 latencies at frontal sites for the retrieval phase [23]; results that point to a greater effort required by LD children since the P300 amplitude is considered a marker of the amount of attentional resources required to perform a cognitive task [24]. Moreover, when the WM-related power spectrum of healthy children was compared with adults [25], the children showed more delta, more theta, and less alpha power; EEG patterns which the authors interpreted as compensatory mechanisms due to neural immaturity. These findings are supported by a work that compared LD children with healthy control children in a task-related power-spectrum analysis of the maintenance phase of a WM task [26]. Children with LD group showed a slower overall activity with more delta and theta power, and less gamma power at posterior brain sites; patterns of activity considered as indices of inefficient neural resource management to achieve proper cognitive performance. In EEG studies during cognitive tasks, the delta activity has been implied with states of sustained concentration coupled with the inhibition of sensory information [25, 27–29]. Higher task-related theta power is more pronounced in less apt individuals, at greater task difficulties including conditions that require a higher WM load with more items to memorize, and in situations in which the focusing of attention involves more effort [30–35]; hence, the task-related theta power is considered to be increasingly recruited according to the neural resources needed to properly perform a cognitive task. And for the gamma band, a sustained increase over posterior sites is involved with a role of memory maintenance and the binding of memory representations [36–40]. Thus, the previous findings point to greater recruitment of delta and theta power and less recruitment of the high-frequency gamma band, in conditions of a higher WM load and less mature populations with greater difficulties to perform WM tasks.

For the treatment of LD, the main interventions used are special education classes and evidence-based programs of reading, writing, or mathematics [41–43]. Also, surging from the EEG field of research, a Neurofeedback (NFB) treatment is a relevant therapeutic approach. NFB is an operant conditioning training aimed at modifying the brain activity with therapeutic or

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performance-enhancing aims [44–46]. A NFB treatment still occupies an experimental treatment status [47]; with ongoing research of its effects in many disorders such as attention-deficit/hyperactivity disorder, anxiety disorders, epilepsy, among others; including LD [48–50]. The current research of NFB effects in LD children has shown that a protocol aimed at normalizing their altered EEG resting-state by reinforcing the reduction of a theta/alpha ratio [50] is capable of boosting the cognitive-behavioral performance and improving resting-state EEG patterns by reducing such ratio of abnormally slower activity; with treatment effects lasting for at least two years [51]. These positive effects suggest a facilitation of the EEG maturation due to this NFB treatment. Two other works have also found NFB benefits in LD such as an improved spelling and an increased EEG connectivity of the alpha-band with a measure of coherence [49]; and improved measures of reading, phonological awareness, and a normalization of EEG coherence measures [48].

Given that WM is frequently affected in children with LD, and NFB treatments appear to boost cognitive-behavioral performance and regulate their resting-state EEG, the goal of the present work was to examine the effects of a NFB treatment (theta/alpha inhibition at lead with the most abnormal theta/alpha ratio) on the WM-related EEG power spectrum of children with LD. Specifically, we aimed to analyze the WM-power spectrum of LD children during the maintenance phase of a Sternberg-type WM task, as the pre-post treatment comparison of two groups: a NFB group *vs.* a sham-NFB group. Our main hypothesis being of the NFB treatment as inducing a tendency to normalize the EEG task-related WM power spectrum; by decreasing the excessively slower EEG power in the delta and theta bands and increasing the high-frequency gamma activity, as indices of EEG patterns related with better cognitive performance (Martínez-Briones et al., 2020).

2. Materials and Methods

The Ethics Committee of the Instituto de Neurobiología of the Universidad Nacional Autónoma de México (UNAM) approved the experimental protocol on July 1, 2015 [INEU/SA/CB/146], which followed the Ethical Principles for Medical Research Involving Human Subjects established by the Declaration of Helsinki [52]. Informed consent was signed by all the children and their parents.

2.1. Participants

Eighteen right-handed children (11 boys, 7 girls) aged 8 to 11 years diagnosed with LD (see inclusion criteria below) were selected from a larger sample of children referred by social workers from several elementary schools in Querétaro, México. The sample was randomly divided into two groups: 10 LD-children went through a NFB (theta/alpha ratio) treatment and 8 LD-children went through a placebo-sham-NFB treatment (Sham group). Both treatments consisted of 30 training sessions three times a week with a duration of 30 minutes per session. Before and after the treatments, all the children were examined with various tests (including the Sternberg-type WM task) described below.

All children fulfilled the following inclusion criteria: 1) A normal neurological and psychiatric assessment (except for the LD diagnostic requirements as stated below); 2) Intelligence Quotient (IQ) at least of 75, to exclude children with intellectual disability [53]; 3) a parent (mother) with at least a completed elementary school education and a *per capita* income greater than 50 percent of the minimum wage; and 4) an abnormally high EEG theta/alpha ratio compared to a normative database.

The LD diagnosis was established based on the following three criteria: a) poor academic achievement reported by teachers and parents, b) percentiles at 16 or lower in the subscales of reading, writing, and/or mathematics of the Infant Neuropsychological Scale for Children [54] and c) LD diagnosis by a psychologist according to the DSM-5 criteria of LD [2]. Several of them failed on different items in the attentional evaluation of the DSM-V, as it is common in this disorder [55, 56]; but they did not meet the DSM-5 criteria of ADHD [2]. Table 1 shows the pre-treatment characteristics of both groups. The frequency of academic impairments found in our LD sample were as follows: 9 children impaired in the three domains (reading, writing, and mathematics); 3

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children impaired in reading and writing; 2 children impaired in reading and mathematics; 2 children impaired in writing and mathematics; and 2 children impaired in mathematics.

Table 1. Before-treatment sample composition

	NFB group n= 10		Sham group n= 8		Statistical differences between groups
	Mean	**Sd**	**mean**	**sd**	
Age	10.4	1.0	10.1	0.8	t = 0.59, (NS)
WISC test:					
Full Scale IQ	90.1	12.4	89	8.5	t = 0.21, (NS)
WM Index	85	11.7	94.5	13.7	t = -1.58, (NS)
Female/Male ratio	3/7		4/4		OR = 2.33; CI:(0.3, 16.2); (NS)
z Theta/Alpha ratio*	2.6	0.8	2.2	0.6	t = 0.81, (NS)

*The z value of theta/alpha ratio refers to the most abnormal EEG lead.

2.2. Neurofeedback and Sham treatment procedures

All children showed an abnormally high EEG theta/alpha ratio than a resting-state EEG normative database before being randomly assigned to either the NFB or the Sham treatment groups. The resting-state EEG was recorded with eyes closed while seated in a dim-lit faradized and soundproofed room, from 19 leads of the international 10-20 system (ElectroCap, International Inc.; Eaton, Ohio), referenced to linked earlobes (A1-A2). For this purpose, a Medicid™ IV equipment (*Neuronic Mexicana*, *S.A.*; Mexico) and a v5.0 Track Walker™ recording software system were used. The amplifier bandwidth was set between 0.5 and 50 Hz. All electrode impedances were equal to or less than 5 kΩ, and the signal was amplified with a gain of 20,000. The EEG data were sampled every 5 ms and edited offline. Twenty-four artifact-free segments of 2.56 seconds were selected, from which an EEG analysis was performed offline. The fast Fourier transform was applied over the data to obtain the absolute power of each of the following frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz).

To calculate the z-values for the theta/alpha ratio, absolute power (AP) of the theta and alpha bands was computed for each electrode, and a geometric power (Hernandez et al., 1993) was subtracted from the cross-spectral matrix.

The log value (theta AP/alpha AP) was computed, and z-values for this logarithm were calculated using the equation:

$$Z= [\log (\text{thetaAP}/\text{alphaAP}) - \mu] / \sigma$$

where μ and σ are the mean value and the standard deviation, respectively, of a normative sample of the same age as the subject (Szava et al., 1994; Valdés et al., 1990). Since the EEG of children with LD is characterized by having more theta and less alpha power than the EEG of children with typical development, having a z-value greater than 1.645 (1-tailed distribution, $p = 0.05$) in at least one lead was also considered as an added inclusion criterion. The NFB treatment was delivered via the lead with the highest abnormal z-value.

The NFB treatment was applied using a neurofeedback program adapted for the Medicid IV registration system. A threshold level was selected in which the subject obtained a reward between 60 and 80% of the time. The stimulus used as a reward was a tone of 500 Hz at 60 dB. Every 3 minutes, the threshold level was updated based on the subject's performance. Each subject received 30 training sessions three times a week, and the duration of each session was 30 minutes. The Sham treatment was identical to the NFB treatment, except that the reward was delivered randomly, noncontingent on EEG activity.

2.3. Working Memory Task

The WM task used in this work was a modified version of the Sternberg memory task [22], a classic task that allows to assess each phase of the WM process (encoding, maintenance, and retrieval). A verbal version of this task was employed since LD children show a more consistent deficit in the phonological loop subsystem of the Baddeley´s WM model [6, 8].

The WM task (Figure 1) consisted of two conditions (low-load and high-load) presented in 180 trials, with 90 trials per condition appearing randomly. At each trial, four digits appeared simultaneously on the screen after a warning signal (asterisk). In the low load condition, all the digits were the same; in the high load condition, the digits were different and not in ascending or descending order, neither pure even nor pure odd. The participants were instructed to memorize the numbers since after the four-digits set appeared, a single-digit (probe stimulus) is presented; they had to press one button (match response) if the digit was included in that trial and press another button if not (non-match response). To perform the power spectrum analysis, segments of 800 ms were selected in the WM maintenance phase, only in trials with correct answers. Stimuli were presented with the software MindTracer [57] and synchronized with the EEG data acquisition system. This WM task was administered twice for both groups: Before the treatment (NFB or Sham) and two months after the treatment.

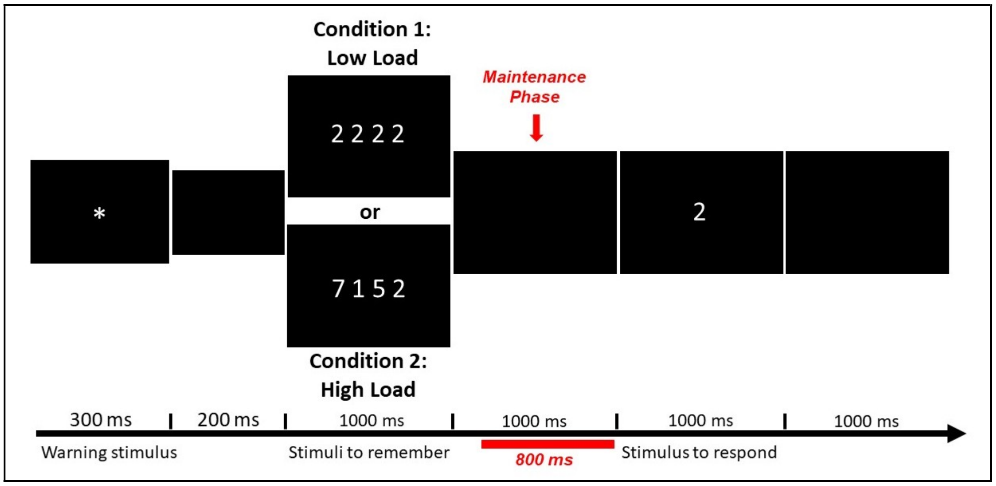

Figure 1. Representation of a single trial (both conditions have been represented in the same Figure). In this case, the single digit ('probe stimulus') was included previously in the set 'stimuli to remember' from both conditions, and the subject had to press the button of the 'match response'. The segment in red corresponds to the WM maintenance phase, the section selected for the power spectrum analysis. The total trial duration is 4500 msec.

2.4. EEG recording and data analysis of the WM task

Before and after the treatments, the administration of the WM task was coupled with an EEG of similar specifications to the resting-state condition: All the children were seated in the dim-lit faradized and soundproofed room. The task-related EEG was recorded during the task performance (with eyes open) using the Medicid IV and Track Walker™ v5.0 data systems, from 19 leads of the 10–20 system referenced to the linked earlobes (A1–A2). The amplifier bandwidth was set between 0.1 and 50 Hz. The signal was amplified with a gain of 20,000 with electrode impedances at or below 5 kΩ, and the EEG data was sampled every 5 ms with a sampling frequency of 200 Hz.

For the power spectrum calculation, 800 ms of the WM maintenance phase from each trial with correct responses were used. Up to 90 trials were recorded per condition (to guarantee a necessary number of EEG epochs to analyze). From which we admitted a minimum of 19 artifact-free segments for the power spectrum analysis. This number of epochs assures, in one hand, the smoothness of the power spectrum and, on the other hand, that the cross-spectral matrix is positively defined (at least as many segments as EEG leads are needed to achieve this condition), a requirement for the subsequent processing and statistical analyses [58]. The recordings were edited off-line by an expert neurophysiologist, who selected only artifact-free and quasi-stationary epochs before the probe-stimuli onsets, without using any automatic algorithm for artifact rejection. The automatic artifact rejection is useful in high-density EEG recordings, where the visual inspection of the data becomes difficult and controversial, as well as to obtain a clean recording of all channels during long periods. However, since our recordings contain the standard setting of 19 electrodes, we prefer to keep control of the recording conditions to obtain clean recordings and avoiding the use of automatic procedures, which are not 100% percent guaranteed to produce a clean signal and which may also introduce undesirable effects in the "cleaned" signal.

The classic approaches to analyze the EEG voltage at the sensor space (over the scalp) have two main drawbacks: the volume conduction effect and the reference electrode effect, both inducing mixing of signals that distort the real neurophysiological events [59]. These shortcomings can be partially solved by source localization techniques, which diminish possible localization errors and overcome the sensor space limitations by analyzing the contribution of specific cortical brain areas [60, 61].

To attenuate the well-known leakage (mixing) problem of the EEG signals at the scalp due to volume conduction [62], we performed our power spectrum analysis at the estimated primary current sources. For this, we first apply the *s-Loreta* technique [61], which transfers our data from 19 leads to a high-resolution volumetric grid of 3244 sources. However, as stated in Biscay et al. [63], besides the difficulty of analyzing such high number of sources, there is the limitation that only a small number of sources can be independently estimated for a given number of EEG sensors; specifically, the maximum number of independent sources after solving the inverse problem by any linear method is the number of EEG sensors minus 1. In their paper, they also presented an algorithm that, under quite mild assumptions, can completely unmix the signals for that small number of sources when their domains are specified as corresponding to given regions of interest (ROIs) of said high-resolution grid. In the present paper, we adhere to that methodology.

Before estimating the power spectrum at the sources using *s-Loreta*, the EEG data recorded with the linked earlobes reference is re-referenced to the Average Reference montage. This step solves two drawbacks: a) the possible effect induced by possible unequal impedances between the two earlobes and b) the primary current estimated at the sources employing *s-Loreta* is reference-free [61].

In the EEG literature, in order to choose the specific sources (or ROIs) for the power spectrum analysis, it is frequent to use one of the following methods: 1) A selection based on prior alleged knowledge of brain functioning, such as working memory networks previously identified through neuroimaging [64]. 2) A selection of the sources closer to the 10-20 leads, which is not technically arbitrary since the source localization methods are usually more precise in the regions closer to the sensors; 3) a data-driven approach where the ROIs are selected based on the intrinsic variability of the data. The first two methods are not optimal since they ignore the data itself and do not provide the real brain areas involved in a specific experimental task. In this work, we used a data-driven approach based on the eigenvector centrality mapping technique (ECM) [65] adapted to the present work by the authors.

The ECM is a technique based on calculating of the principal components decomposition of a similarity matrix, usually based on the signal in the time domain over all the voxels. It computes its first principal component and interprets each entry of this vector as an index of global connectivity for the corresponding brain voxel. The voxels with the higher connectivity indexes are considered the most connected voxels in the brain. In general, the ECM method is calculated for each subject separately, and for group analysis, a statistical test is performed among the subjects to select those voxels with a high connectivity index in most subjects. In our case, we constructed the similarity matrix as the one formed by the absolute values of the correlations between the sources of all voxels. We developed an optimized version of the power method algorithm in terms of memory usage and CPU intensity, which can obtain the first principal component for all the subjects at the same time. In this way, it is not required to perform a statistical analysis to select the most connected voxels since the global connectivity index that comes out from our approach is a group index of connectivity; and the voxels with a high global connectivity index will be common for most of the subjects. With this index of global connectivity obtained by the above-described procedure, 18 ROIs (the number of scalp sensors minus 1) were selected. More specifically, not only the sources identified by this index

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were obtained, but we also included the equivalent sources in the contralateral hemisphere in the cases when they were not selected according to their values of the connectivity index. The reason for this addition was to be able to compare how the homologous sources in both hemispheres participated in the task. Figure 2 shows in red the 18 selected ROIs by the data-driven approach, also published by Martínez-Briones et al. [26]. For a better insight into its configuration, the cortex regions nearest to the positions of the sensors at the scalp are also illustrated in blue. Note that many of the relevant areas detected by our algorithm are far from the sources immediately below the scalp sensors. The source signals at the 18 ROIs were processed by the unmixing algorithm elaborated by Biscay et al. [63]. Then, the segments of unmixed signals of such 18 sources (with 160-time points each) in each condition of all subjects were transformed to the frequency domain with the Fast Fourier Transform. This procedure yielded a source spectrum of 40 frequencies, from 1.25 to 50 *Hz* (frequency bins every 1.25 *Hz*) for every ROI for each subject under each task condition and group.

We performed the statistical analysis of the power spectrum using this narrow band model of 1.25 Hz frequency resolution up to 50 Hz. Nevertheless, in the results and the discussion sections, to consolidate the information and make it easier to understand, we summarized the findings using the classic frequency bands: delta (δ)= 1-4 *Hz*, theta (θ)= 4-8 *Hz*, alpha (α)= 8-12 *Hz*, beta (β)= 12-30 *Hz*, and gamma (γ)= 30-50 *Hz* (the upper extreme of the interval is never reached to avoid overlapping). Gamma band is usually reported up to 100 Hz; however, we report changes up to 50 Hz, which is considered a lower-gamma band, due to our hardware limitations.

Finally, for the main group (NFB or Sham) and task condition (low-load or high-load) comparisons, we used a Linear Mixed Effect Model (LME) [66], in which we tested these factors at each frequency to compare the data before and after the treatments. Independent t-test analyses were also performed for the following variables: Full-scale IQ, WM index, the theta/alpha ratio of the most abnormal EEG lead, and behavioral results (correct responses and response times) of the Sternberg WM task.

To safeguard the statistical significance of our results given the high number of comparisons, the alpha level was corrected using the permutations technique [67]. In all figures that we show in section 3.2 with the results of the statistical significance, the two horizontal lines indicate the upper and lower significance thresholds at p=0.05, corrected by permutations.

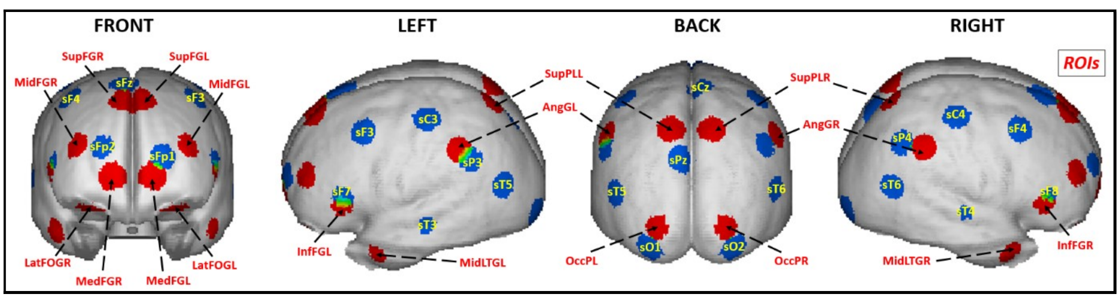

Figure 2. ROIs selected by the populational ECM. The sources closer to the 19 leads are in blue, and the 18 ROIs are in red: LatFOGL, Left lateral orbitofrontal gyrus; LatFOGR, Right lateral orbitofrontal gyrus; MedFGL, Left medial frontal area; MedFGR, Right medial frontal area; InfFGL,Left inferior frontal gyrus; InfFGR, Right inferior frontal gyrus; MidFGL, Left medium frontal gyrus; MidFGR, Right medium frontal gyrus; SupFGL, Left superior frontal gyrus; SupFGR, Right superior frontal gyrus; MidLTGL, Left medial temporal gyrus; MidLTGR, Right medial temporal gyrus; SupPLL, Left superior parietal area; SupPLR, Right superior parietal area; AngGL, Left angular gyrus; AngGR, Right angular gyrus; OccPL, Left occipital pole; OccPR, Right occipital pole. Taken from Martínez-Briones et al. [26]

3. Results

According to the comparison of the main characteristics of both groups (see Table 1), the NFB and Sham groups did not differ in age, gender, IQ, or theta/alpha ratio for the pre-treatment comparison. Therefore, the children of both groups were aptly comparable for the consecutive

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analyses. The IQ measures and the theta/alpha ratio were also of interest for an additional after-treatment comparison between the groups, but they did not statistically differ after the treatments.

3.1. Behavioral results of the WM task

The behavioral results of the WM task are in terms of a percentage of correct responses and the response times of the two conditions (Low-Load and High-Load). There were fewer correct responses and slower response times in the High-Load condition than in the Low-Load condition. This pattern of differences appears for the two groups both before and after treatment, suggesting that the high-load condition is indeed more difficult condition at this behavioral level.

A main analysis of interest, shown in the following two figures, assessed within-group differences for the percentage of correct responses (Figure 3) and response times (Figure 4) by comparing the Before-treatment vs. the After-treatment for each group taken separately. In these comparisons, we did not find before-after statistical differences in the percentage of correct responses for either group, a finding that could point to insufficient sensitivity of the WM task to detect possible improvements in performance at this behavioral level. On the other hand, for the response times, the NFB group did show a faster response time for the High-Load condition after the NFB treatment (t= 2.56, p<0.05). Thus, the NFB treatment seems to modify an index of good performance in terms of an improved velocity of WM retrieval.

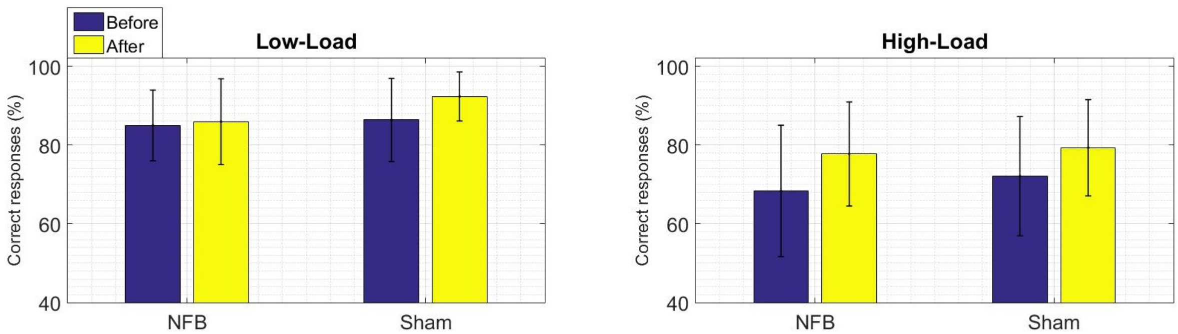

Figure 3. Within-groups behavioral results of the percentage of correct responses for the WM task (the left panel shows the Low-Load condition, the right panel shows the High-Load condition). Mean values of the percentage of correct responses before treatment appear in blue and after treatment appear in yellow. There were no statistical differences for the before *vs.* after treatment comparisons within groups taken separately.

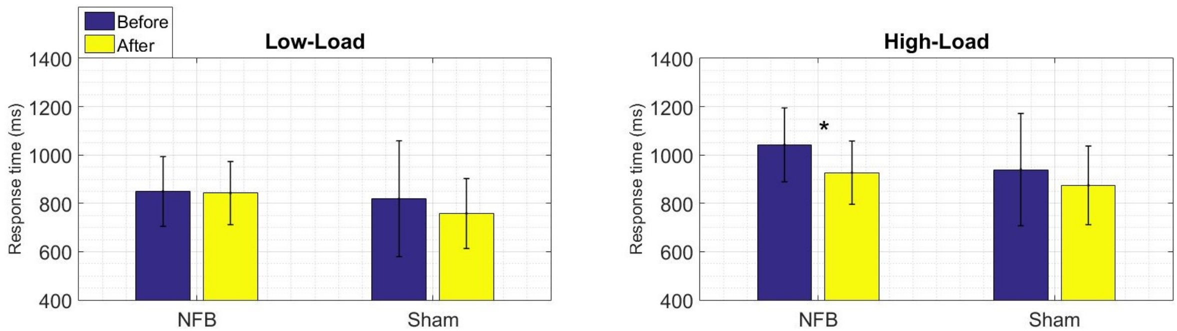

Figure 4. Within-groups behavioral results of the response times for the WM task (the left panel shows the Low-Load condition, the right panel shows the High-Load condition). Mean values of response time before treatment appear in blue, and after treatment appear in yellow. The asterisk indicates statistically significant differences in the before *vs.* after treatment comparison of the NFB group for the High-load condition (t= 2.56, *p<0.05).

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3.2. WM-related Power Spectrum results

In the figures below, we focus the power-spectrum analyses on the more difficult High-Load condition, given that our within-groups High-Load vs. Load-Load comparisons did not show statistical differences at this power-spectrum level. Figure 5 shows the power spectrum within-group differences for the NFB group by comparing the Before-treatment vs. the After-treatment conditions. Figure 6 shows this Before-After treatment comparison for the Sham group. Looking at both figures, a higher beta and gamma power after-treatment at the right medial temporal gyrus in both groups can be appreciated. The NFB group (figure 5) also shows an increased gamma power at the superior parietal areas and reduced beta power at the occipital poles of both hemispheres after treatment. On the other hand, the Sham group (figure 6) shows a right hemisphere higher beta power in the right lateral orbitofrontal gyrus, the right medium and superior frontal gyri, and the right occipital pole coupled with also a higher gamma power for the after-treatment condition; another finding in the Sham group was the reduction of the frontal delta and theta power (in the left orbitofrontal gyrus and the bilateral medial frontal areas). Therefore, the NFB group shows a more selective modulation of the high-frequency bands in the shape of a decreased beta and an increased posterior gamma power after the NFB treatment; and the Sham group shows mostly a decrease in the delta and theta power of frontal areas and an increased beta power after the Sham-NFB sessions.

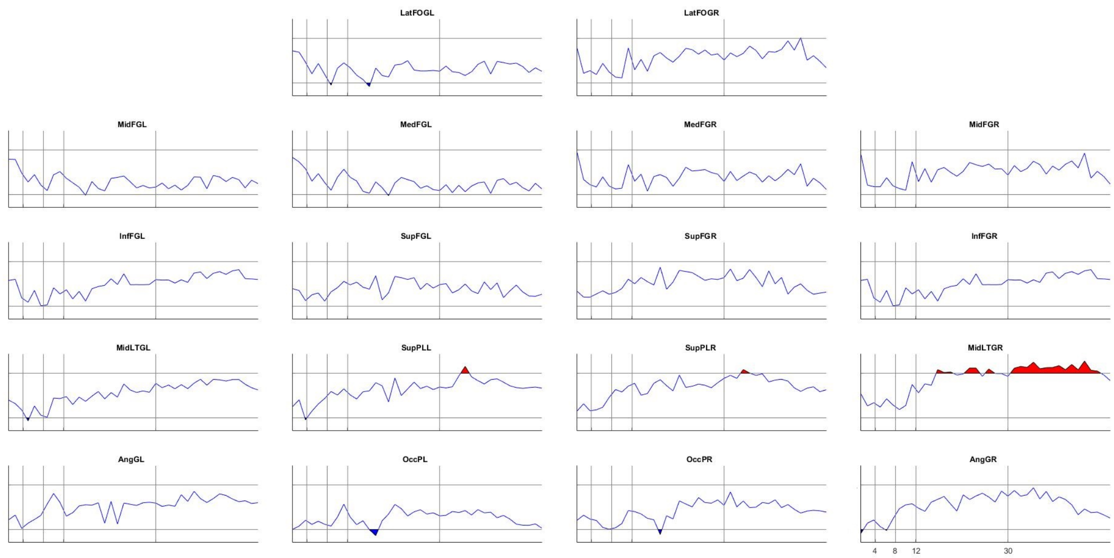

Figure 5. Power-spectrum differences within the NFB group in a before *vs.* after treatment comparison of the WM High-Load. The *X-axis* represents the frequencies (1.25-50 *Hz*), separated by vertical lines to the classic frequency bands: delta (δ)= 1-4 *Hz*, theta (θ)= 4-8 *Hz*, alpha (α)= 8-12 *Hz*, beta (β)= 12-30 *Hz, and* gamma (γ)= 30-50 *Hz (open upper intervals)*. The *Y-axis* represents the t-values of the LME procedure. The red patches (above the horizontal lines) indicate a higher power for the after-treatment condition than for the before-treatment condition (p*<0.05, randomization-corrected). The blue patches (below the horizontal lines) indicate a higher power for the before-treatment condition (p*<0.05, randomization-corrected). *LatFOGL/LatFOGR:* Left/Right lateral orbitofrontal gyrus; *MedFGL/MedFGR:* Left/Right medial frontal area; *InfFGL/InfFGR:* Left/Right inferior frontal gyrus; *MidFGL/MidFGR:* Left/Right medium frontal gyrus; *SupFGL/SupFGR:* Left/Right superior frontal gyrus; *MidLTGL/MidLTGR:* Left/Right medial temporal gyrus; *SupPLL/SupPLR:* Left/Right superior parietal area; *AngGL/AngGR:* Left angular gyrus; *OccPL/OccPR:* Left/Right occipital pole.

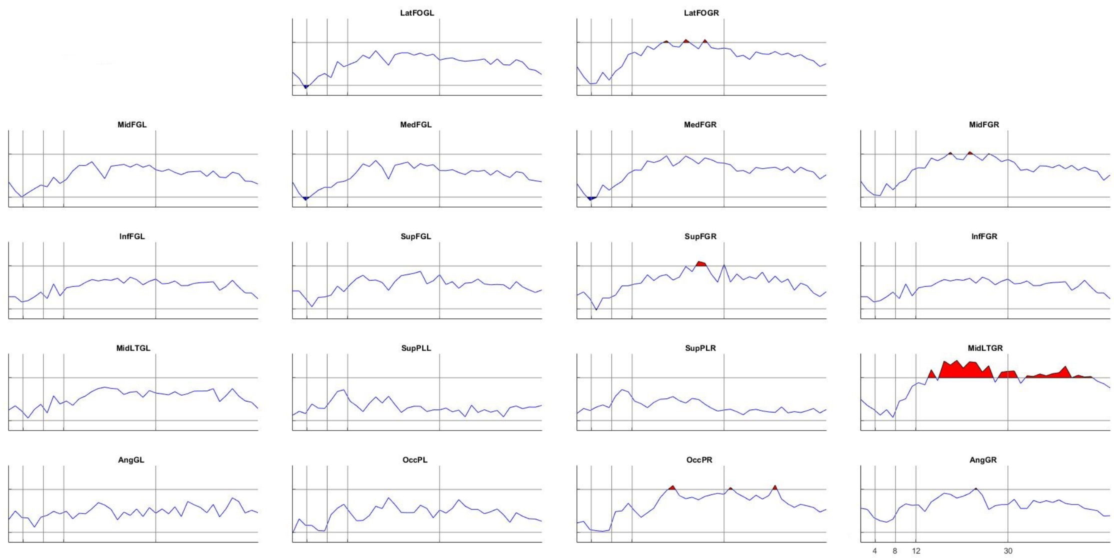

Figure 6. Power-spectrum differences within the Sham group in a before *vs.* after treatment comparison of the WM High-Load. The *X-axis* represents the frequencies (1.25-50 *Hz*), separated by vertical lines to the classic frequency bands: delta (δ)= 1-4 *Hz*, theta (θ)= 4-8 *Hz*, alpha (α)= 8-12 *Hz*, beta (β)= 12-30 *Hz, and* gamma (γ)= 30-50 *Hz (open upper intervals)*. The *Y-axis* represents the t-values of the LME procedure. The red patches (above the horizontal lines) indicate a higher power for the after-treatment condition than for the before-treatment condition (p*<0.05, randomization-corrected). The blue patches (below the horizontal lines) indicate a higher power for the before-treatment condition (p*<0.05, randomization-corrected). *LatFOGL/LatFOGR:* Left/Right lateral orbitofrontal gyrus; *MedFGL/MedFGR:* Left/Right medial frontal area; *InfFGL/InfFGR:* Left/Right inferior frontal gyrus; *MidFGL/MidFGR:* Left/Right medium frontal gyrus; *SupFGL/SupFGR:* Left/Right superior frontal gyrus; *MidLTGL/MidLTGR:* Left/Right medial temporal gyrus; *SupPLL/SupPLR:* Left/Right superior parietal area; *AngGL/AngGR:* Left angular gyrus; *OccPL/OccPR:* Left/Right occipital pole.

An analysis of particular interest was a between-groups (NFB *vs*. Sham) comparison after subtracting before from after treatment data of each separate group, producing an 'after minus before' variable for the contrast between the groups (figure 7). This comparison was performed for both its value as a direct between-groups contrast and to isolate the actual contributions of the NFB treatment, given that the Sham procedures are known to also produce some positive effects in the subjects [68, 69]. The results that this analysis yielded were: 1) a higher gamma power for the NFB group at the bilateral superior parietal areas, compared to the Sham group; and 2) less right beta power at the orbitofrontal gyrus, the medial frontal area, and the right occipital pole for the NFB group (compared to the Sham group). According to the main hypothesis, these overall patterns of power-spectrum differences for both the before vs. after treatment and the NFB vs. Sham groups were partially expected and will be thoroughly discussed in the following section.

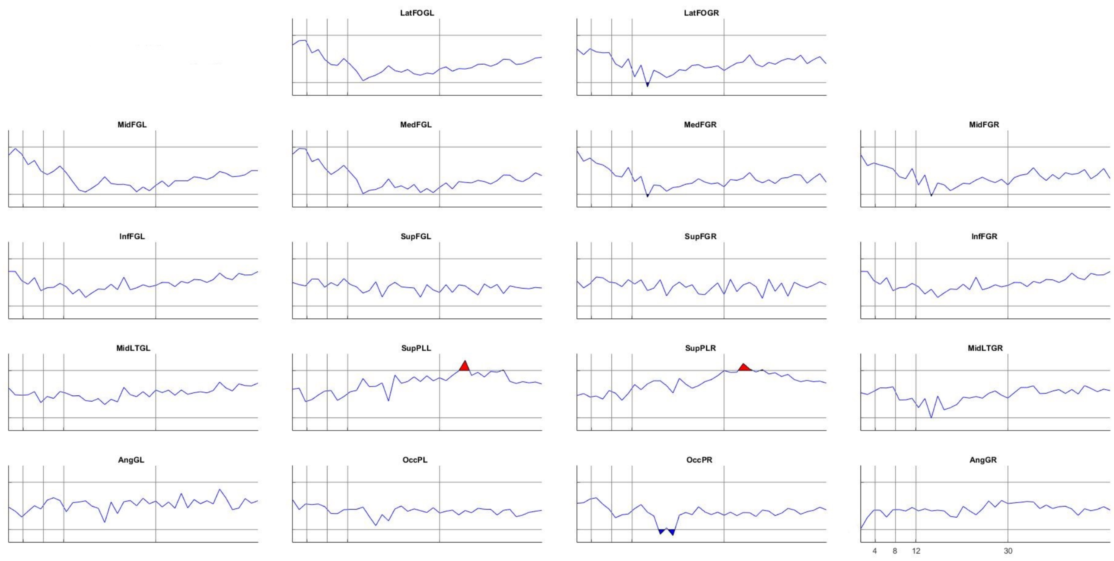

Figure 7. Power-spectrum differences between the groups (NFB *vs*. Sham) for the High-Load after subtracting the before-treatment from the after-treatment condition (yielding an 'after minus before' condition of group comparisons). The *X-axis* represents the frequencies (1.25-50 *Hz*), separated by vertical lines to the classic frequency bands: delta (δ)= 1-4 *Hz*, theta (θ)= 4-8 *Hz*, alpha (α)= 8-12 *Hz*, beta (β)= 12-30 *Hz, and* gamma (γ)= 30-50 *Hz (open upper intervals)*. The *Y-axis* represents the t-values of the LME procedure. The red patches (above the horizontal lines) indicate a higher power for the NFB group than for the Sham group (p*<0.05, randomization-corrected). The blue patches (below the horizontal lines) indicate a higher power for the Sham group (p*<0.05, randomization-corrected). *LatFOGL/LatFOGR:* Left/Right lateral orbitofrontal gyrus; *MedFGL/MedFGR:* Left/Right medial frontal area; *InfFGL/InfFGR:* Left/Right inferior frontal gyrus; *MidFGL/MidFGR:* Left/Right medium frontal gyrus; *SupFGL/SupFGR:* Left/Right superior frontal gyrus; *MidLTGL/MidLTGR:* Left/Right medial temporal gyrus; *SupPLL/SupPLR:* Left/Right superior parietal area; *AngGL/AngGR:* Left angular gyrus; *OccPL/OccPR:* Left/Right occipital pole.

4. Discussion

Our purpose was to explore the effects of a NFB treatment on the WM processing of children with LD with theta/alpha excess in their resting-state EEG. For this, we compared the behavior and the WM-related power spectrum between a group of children with LD who received a NFB treatment and another group of LD children who were given a Sham-NFB treatment.

In a pre-treatment descriptive comparison of the groups, we did not find statistical differences for the main variables of age, gender, IQ (including a WM index provided by the WISC test), for the theta/alpha ratio, or the WM behavioral performance (correct responses and response times). Thus, our random assignment of children with LD successfully ensured that our groups were comparable in the following WM post-treatment behavioral and power spectrum results. Our primary outcomes of interest are those regarding our selected Sternberg memory task both at the behavioral and the EEG level. However, it must be noted that neither group showed an improvement in IQ, WM index, or theta/alpha ratio post-treatment. The main reason for measuring IQ in this study was to satisfy the criterion for the diagnosis that establishes that the learning difficulties are not better accounted for by intellectual disabilities (American Psychiatric Association, 2013). In general, the IQ is a rigid measure with a high rate of failure to be improved by therapies or programs with performance-enhancing aims [70–72]; thus, our negative finding was likely to occur. Schooling/education has been found to improve the IQ of subjects with typical development at 1-5 points for every additional year of education [73]. Since this does not usually happen in LD children, this realization only adds to the importance of finding out more about possible treatments for LD

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subjects that both struggle at school and whose usual WM impairments also contribute to their academic problems [14].

Regarding the lack of a theta/alpha ratio improvement, there may be various explanations. Although in previous studies of our research group using this NFB protocol we always found a reduction (in average) of the theta/alpha ratio (Fernández et al., 2003, 2007, 2016), this finding was not common to all individuals who received the NFB treatment [74]. Also, on the one hand, the sample sizes in this study could be too small to make the change evident, especially if there was high within-group variability. On the other hand, there is evidence of changes in behavior without changes in the EEG after a NFB treatment [50, 75, 76]. In previous studies, we have interpreted this as the NFB treatment modifying the functioning of subcortical structures, which would be reflected in behavior, but not necessarily in cortical postsynaptic activity. Thus it would be unlikely to observe EEG changes since 97% of the recorded EEG activity originates in the cortex [59, 77]. Yet these functional changes of deep structures could later modify the EEG through the modulation of thalamic-cortical circuits [51, 78]. In addition to the evidence shown by Fernández et al. [50] in LD, Lubar et al. [75] in ADHD, and Sterman & Egner [76] in epilepsy; there is indirect evidence that by regulating a range of frequencies in the EEG for a single lead, the final changes are observed in other frequencies and different regions, which points to a certain non-specificity of frequency and location effects in NFB. All in all, for future studies we aim to provide finer measures of NFB improvement such as an EEG-NFB at the sources; or arrangements consisting of reinforcing more than one abnormal lead either at the EEG surface level or at the sources too [79].

As to the behavioral results of the WM task, besides the expected Low-Load *vs.* High-Load within-group differences in both the correct responses and response time measures [26]; our additional statistical comparisons yielded a main difference found just for the NFB group: In the pre-post treatment comparison of each separate group, the NFB group showed a faster response time for the High-Load condition after the NFB treatment, with no statistical differences in the percentage of correct responses. Hence, the NFB treatment appears to improve the speed of WM retrieval in children with LD. A good WM performance is required for proper academic achievement, and a better response time in a task that involves memorizing digits is a noteworthy finding.

The WM-related power spectrum analysis was realized not in the sensor space but for 18 source ROIs. An adapted eigenvector centrality mapping (ECM) technique was used as a data-driven procedure to select the ROIs. This yielded a global index of connectivity for each voxel that allowed a more robust algorithm for ROIs selection. This data-driven procedure is a valuable ROIs selection approach by avoiding the assumption of arbitrary or uninformed criteria such as choosing the sources closer to the leads; or supposed prior knowledge of brain structure or function, such as an alleged WM network that could not apply to LD children with insufficiently mapped task-related neural correlates, or who possibly employ a different strategy to solve a task. By contrast, our ROIs broadly underlie the sample variance as active sites present in the children during the maintenance phase of the WM performance. A main result from this approach was of many ROIs settled in prefrontal areas, with no ROIs selected in the central cortex, i.e., near the Cz, C3, and C4 leads. This finding agrees with other task-related EEG studies that do not identify a contribution of central areas during a cognitive performance; while mainly frontal and posterior regions have indeed been involved in the WM functioning [34, 80, 81].

Regarding the power spectrum analyses during the maintenance phase of the WM task, we first examined each group taken separately in a within-group before *vs.* after treatment comparison. Our original hypotheses were of NFB inducing a tendency to normalize the WM-related power spectrum by diminishing the excess of delta and theta power while increasing the gamma activity. We found these predicted patterns but distributed between the groups and with some differences for the beta band. For example, the NFB group showed specific high-frequency changes with an increased gamma power at posterior areas (and a decreased beta activity), while the Sham group completed this picture with the decrease of delta and theta power at frontal areas (and increased beta activity). An improvement in performance by a sham-NFB or a placebo treatment has been an acknowledged

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phenomenon and a recently recurring criticism of the NFB literature, with a renewed insistence on using appropriate control groups and analyses to isolate the experimental effects [68, 69]. This problem was partially solved by our between-group comparison in which we attempted to isolate the proper NFB effects. With this additional comparison between the groups, the changes observed in delta and theta for the Sham group disappeared among the groups; and for the NFB group, it was now highlighted a gamma power increase at the posterior areas and a beta power decrease at the right hemisphere, compared to the Sham group. The gamma activity has been attributed to a role of memory maintenance and the binding of memory representations [39, 40], and frontal and central beta activity has been related to the preparation of motor responses [27]. Given the lack of finesse of our experimental paradigm to detect the binding of memory representations, and the fact that our power spectrum analysis was performed over EEG segments taken in the maintenance phase, we assume that the increased gamma power of the NFB group reveals improved memory maintenance due to the NFB treatment, a finding that could also be an EEG substrate of the improved speed of WM retrieval for this same group of children. On the other hand, the decreased beta activity in the NFB group takes a more equivocal form. A workable explanation of the beta power changes can be advanced considering them as nonspecific NFB treatment effects [82] that could share with other anxiety-reducing therapeutic interventions such as forms of meditation including mindfulness training. There has been conflicting evidence of beta power changes after meditation programs, with some increases and mainly decreases of beta power [83, 84]. The decrease of beta is considered an effect of transcendental meditation and an index of 'thoughtless emptiness', an important aim to achieve in meditation practices. Thus, a decreased beta power after the NFB treatment could signify a nonspecific effect of anxiety reduction for our LD children. Also, from the sham group point of view regarding its beta power increase, possible adverse effects have been reported for Sham-NFB interventions such as the occurrence of learned helplessness [85], inducing higher levels of restlessness or anxiety by the nature of the noncontingent random reward that fails to be predicted by the child. Hence, the increased beta activity for the Sham group could otherwise be due to an expectancy effect that elicits an anxious motor preparation to respond by these children.

To conclude, this is the first study of the effects of a NFB treatment in WM measures (at the behavioral and the EEG power spectrum levels), showing promising positive results in variables such as improved response times post-treatment and an increased gamma power at the parietal areas coupled with a decreased beta power by the NFB treatment. We explicate these power spectrum patterns of a boost in the gamma band as revealing improved maintenance of memory representations due to NFB; coupled with the decreased beta band as an index of reduced anxiety. Our group has previously found positive results of NFB in LD children over a two-year follow-up [51] and we also aim to follow through with this verification step for our WM results.

Author Contributions: Conceptualization, Benito Martínez-Briones and Thalía Fernández; Data curation, Benito Martínez-Briones, Lucero Albarrán-Cárdenas and Thalía Fernández; Formal analysis, Benito Martínez-Briones, Jorge Bosch-Bayard and Thalía Fernández; Funding acquisition, Jorge Bosch-Bayard and Thalía Fernández; Investigation, Benito Martínez-Briones, Jorge Bosch-Bayard, Rolando Biscay-Lirio, Lucero Albarrán-Cárdenas, Juan Silva-Pereyra and Thalía Fernández; Methodology, Benito Martínez-Briones, Jorge Bosch-Bayard, Rolando Biscay-Lirio, Lucero Albarrán-Cárdenas, Juan Silva-Pereyra and Thalía Fernández; Project administration, Thalía Fernández; Resources, Jorge Bosch-Bayard and Thalía Fernández; Software, Benito Martínez-Briones, Jorge Bosch-Bayard and Rolando Biscay-Lirio; Supervision, Jorge Bosch-Bayard, Rolando Biscay-Lirio, Juan Silva-Pereyra and Thalía Fernández; Validation, Benito Martínez-Briones and Rolando Biscay-Lirio; Visualization, Benito Martínez-Briones and Jorge Bosch-Bayard; Writing – original draft, Benito Martínez-Briones; Writing – review & editing, Benito Martínez-Briones, Jorge Bosch-Bayard, Rolando Biscay-Lirio, Lucero Albarrán-Cárdenas, Juan Silva-Pereyra and Thalía Fernández.

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