

Article

Progress Report in Neuroscience and Education: Experiment of Four Neuropedagogical Methods

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Abstract: We endeavor through this work to demonstrate the effects of the introduction of neuroeducation data in schools and their application, via an experiment of neuropedagogical methods, to respond to the hypothesis that the contribution of neuroeducation may be beneficial for learning. During this study we designed four neuropedagogical methods and to measure their effect on the learning of students in the classroom we used an evaluation grid comprising six psychopedagogical parameters. The results show that no statistically significant variation of these psychoeducational parameters is observed between sexes. However, a variation is recorded for the four neuropedagogical methods between the groups in pre-test and post at the levels of the mean scores ranging from 5.15% to 440%.

Keywords: neuroeducation; neurolearning; engagement; attention; memory; return on error



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1. Introduction

The creation of “neuroeducator” training, first proposed 30 years ago [1], was based on the belief that brain science could transform and improve teacher practice. However, the role of neuroscience in education is still under discussion [2,3]. The educational research community has not finished defining and conceptualizing a science of learning and education [4]. Bridges have been crossed to connect neuroscience and education, for example, long bridges [5], double track bridges [6], bridges over troubled waters [7], and others can be built to make connections between education and cognitive neuroscience. These bridges can be beneficial to both educators and neuroscientists, helping to ask critical questions about the learning brain and providing guidance on where to answer them (bridges over troubled waters education and cognitive neuroscience) [7].

Neuroeducation unites education and neuroscience. Neuroscience, in its broadest sense, studies the processes by which the brain learns and remembers at the molecular and cellular levels (for example, the system of neural areas and pathways underlying our ability to speak and understand language). It seems timely then, to consider how we might apply our increased understanding of brain function and development to explore educational questions [8]. Studies of brain function can contribute, alongside behavioral data, to an understanding of underlying learning processes, and may lead to improved teaching and learning [9].

Currently, one of the challenges of educational neuroscience is the improvement of scientific dialogue and creation of a more widely shared language in educational and neuroscientific circles. Hence the need for professionals who are proficient in shared communication across disciplines [10]. Although policy makers are calling for “scientifically sound practice”, there is little consensus on the conceptual and methodological underpinnings of these research efforts. Part of the challenge stems from the need to balance

academic freedom with clear research standards and to establish principles that allow for the generalization and in-depth evaluation of educationally relevant research findings while maintaining the integrity of each field.

These problems are complicated when pedagogically relevant research from different academic disciplines is examined and attempts at integration are undertaken. In the context of bridging cognitive neuroscience and education, it is important to assess the differences and similarities in methodology, approach, and conceptualization of scientific research between what might be called “traditional pedagogical research” and “traditional cognitive neuroscience research” [7].

Numerous studies have questioned the ways in which neuroscience can be applied in the classroom. The entry of neuroscience into the world of education is felt to be an overbearing intrusion. The difficulty is even greater in defining a disciplinary field that still does not exist as such at the university [11]. Neuroeducation does not yet have an academic status in its own right, its title and definition are not yet unanimously accepted, which is why the marriage between cognitive neuroscience and conventional teaching still seems difficult [12]. The real challenge, then, is to translate laboratory results into strategies to improve learning when establishing links between research and practice is not always easy [13].

Recent brain imaging techniques make it possible to explore the effects of certain types of teaching on the brains of students. The example of reading by grapheme or phoneme with regard to [14] dyslexia and dyscalculia [15] clearly demonstrates this. This encounter between neuroscience and education has given rise to a new research discipline, “neuroeducation” [16–19]. Research in this area of neuroeducation is recent, but the results are of scientific value and of interest to many educators. Although the brain mechanisms involved in learning to read and compute are fairly well known, the effects on the brain of teaching practices associated with these skills remain largely unknown [20].

It therefore seems appropriate to consider how to apply an understanding of brain development and function to explore educational issues [21]. Cruickshank [1] proposed the creation of a neuroeducator profile, on the basis that understanding the brain could improve teacher practice. Neuroscience provides a biologically-based mechanistic approach that could explain why these practices work, suggest additional new approaches [22], and indicate which neural functions are typical or impaired and how they work; but this knowledge must be translated by pedagogical principles into interventions which can be evaluated for effectiveness by behavioral testing in educational settings [9]. Much water has flowed under the “bridge” since Bruer’s argument [5] that a direct brain-behavior-education link was a “bridge too far”. Research findings in mind and cognitive psychology are building that bridge [14,19,23,24].

Research in the area of neuroeducation is recent, but the results are of scientific value and of interest to many educators. Although the brain mechanisms involved in learning to read and calculate are fairly well known, the effects on the brain of the teaching practices associated with these skills remain very little known [20]. Certainly, the debate between neuroscience and education is always lively, but this relationship can be more fruitful when it favors a two-way exchange of ideas and approaches

2. Materials and Methods

2.1. Characteristics of the Sample

The study involved a total of 239 students (aged 12 to 18) divided into 8 classes and 4 subjects in three secondary schools (Moulay Idriss Premier high school, Fechtali high school and Al Andalouss middle school) in Casablanca with the collaboration of 3 administrative staff and 4 secondary school teachers (1 female and 3 male). They all gave their consent to collaborate in this experiment, were between 25 and 57 years of age, and had less than 6 years of experience.

The students were reassured, informed, and prepared to behave as naturally as possible with a stranger in their classroom.

Before starting the experiment interviews were carried out. A first exploratory interview with the administrative managers of the three schools was carried out in order to prepare the field of experimentation. This allowed us to define the list of teachers who would agree to participate in the experiment. In a second step, short training sessions with the teachers were carried out around the following axes: the interest of the study and the contribution of cognitive neurosciences for pedagogy, the principles of learning based on neurosciences, and experiments carried out internationally. Then, with each of the teachers separately, we defined the approach to follow for the proposal of the theoretical sheets and the co-construction of the practical pedagogical sheets, as well as the didactic supports necessary for each lesson. Thus, the sequences that would be used as practice with the control group were defined: two teaching sessions per neuro-pedagogical method, with two pre- and post-test evaluations. This study was carried out with the approval of the educational inspectors and the provincial director, Ben M'sik Sidi Othman.

2.2. Neuropedagogical Methods

2.2.1. Overall Goal of the Methods:

The tool used in this study was a design of four neuro-pedagogical methods inspired by the work of [25–27], whose purpose was to test whether neuroscience research is capable of changing teaching practices to make them more effective, and whether it can help learners take full advantage of their intellectual and affective capacities.

The methods were adapted to our situation and then implemented in the experimental classes while taking into consideration the dimensions of the socio-demographic characteristics of the schools. For each method, we specified the role of the teacher and that of the student during the experiment session (in the form of a sheet).

2.2.2. Experimental Method

- Experimental hypothesis:
- Application material(s):
- Sample:
 - Grade Level(s):
 - Total number of students (G. Exp): number of males, females
- Description of method of experimentation: what the teacher is to do in this experiment, and what the student should do in this experiment (Table 1)
- Student assessment: number of questions, structures, and nature of questions.

2.3. Measuring Instrument

Data were collected through guided observation using a grid to capture the behavior of learners in class during the pre-test session and during the experimental session as a test station according to the proposed instructional sheets. Evaluation grids were duly completed and reviewed with the teacher during the pre-test and post-test sessions to measure the variables as shown in Table 2.

Table 1. Description of teaching methods.

Purpose of the Method	Pedagogical Activities	Roles of the Teacher and the Student
Developing active engagement	1. Role playing	The teacher explains the scientific notions related to the concept of the lesson (photosynthesis) and then distributes the roles. Each student represents the role of an organelle or an element that comes into play in the process of photosynthesis. The teacher orchestrates the game, ensuring that the students respect each other and the time.

Table 1. Cont.

Purpose of the Method	Pedagogical Activities	Roles of the Teacher and the Student
Fostering involvement and motivation, developing personal effectiveness	2. The expert student	In the first instance small production groups are formed and composed by free choice. The members of each group have to choose a part of the course during a previous session with their teacher, which they will prepare at home. In class, during the course session, the members of the group of the same part are called to discuss it, enrich it, and improve its presentation, so that each of them becomes an "expert". In a second phase, the experts of the different parts of the course are formed into "synthesis islands", which exchange ideas, discuss, and formulate a synthesis. The students must prepare the topics of the course before hand at home in order to understand it, enrich it, and present it better, and to agree on the modalities of work and intervention within the framework of a harmonious distribution of tasks.
Improve attention and working memory	3. Varying information access channels	<ul style="list-style-type: none"> • A video presenting different concepts • A flash simulation to get in touch with the notion or concept to be learned • A real experiment • The software for the simulation • A restitution on the board with the class group
Develop memorization	4. Mind map	To help the student to be in the heart of the learning process and to be an actor of the educational system. According to the OAC approach, as follows: O: detect the characteristics of a learning situation helped by a preliminary questioning (individual or by group or brainstorming) around a documentation or a situation A: study and decode the previous observations, conduct a common research in the same direction, and problematize through comparisons, hypotheses, tests ... C: formulate a definition of a concept or a common course summary (formulation guided by the teacher)

Table 2. Evaluation grid of the experiments conducted.

General Student Information	Technical Information	Variables Measured in Pre-Test and in Post-Test
<ul style="list-style-type: none"> • Sex • Level 	Theory and practical experience	<ol style="list-style-type: none"> 1. Attention 2. Active engagement 3. Return on error 4. Number of words memorized

Variables such as attention and active engagement were measured by direct observation in class during learning activities according to a Likert scale in post-test and pre-test, while the other variables, in this case the number of words memorized, feedback on errors, and grades were measured by a written test at the end of the experimental session and also in two periods post-test and pre-test. Satisfaction of the students toward the method was measured at the end of the experiment according to a Likert scale.

2.4. Data Analysis Process

The information collected was processed using SPSS (Statistical Package for the Social Sciences "25 version"). For quantitative data, we used the Wilcoxon test which is a non-parametric alternative to the t-test for paired samples (pre-test and post-test). This allowed us to test our hypothesis that neuroeducation can help learners develop a more alert brain and enable them to be more active, attentive, motivated, and better able to overcome difficulties, by checking whether the psychoeducational parameters vary significantly

between the pre-test and post-test of the experiment. The significance level is set at ($p < 0.05$).

3. Results

As shown in Tables 3 and 4, no statistically significant variation in psychoeducational parameters is found between the sexes; however, they vary for the six neuroeducational methods between the groups in pre-test and post-test according to the following order: highly significant *** ($p < 0.001$), moderately significant ** ($p < 0.01$), insignificant * ($p < 0.05$), and non-significant ($p \geq 0.05$).

Table 3. Effects of pedagogical approaches on variations in means of psychoeducational parameters.

Neuropedagogical Methods	Period	Psycho-Pedagogical Parameters					
		Attention	Active Engagement	Number of Memorized Keywords	Error Correction	Satisfaction	Result of the Written Test
Role playing (N = 26)	Pre-test	0.92 ± 0.7	1.04 ± 0.8	9.19 ± 3.8	0.65 ± 0.8	0.85 ± 0.5	10.5 ± 3.9
	Post-test	1.38 ± 0.8 *	1.46 ± 0.8 *	13.2 ± 5.2 ***	1.08 ± 1 **	1.65 ± 0.8 ***	13.9 ± 5.1 ***
The expert student (N = 28)	Pre-test	1.37 ± 0.56	1.48 ± 0.64	2.38 ± 10.11	0.71 ± 0.9	1.07 ± 0.47	7.04 ± 6.62
	Post-test	2.00 ± 0.00 ***	2.00 ± 0.00 ***	13.74 ± 1.75 ***	1.18 ± 0.9 *	1.68 ± 0.72 **	12.04 ± 8.04 *
Vary the ways in which information is accessed (N = 38)	Pre-test	37 ± 0.6	0.45 ± 0.7	6.21 ± 3.9	0.32 ± 0.6	0.37 ± 0.6	6.92 ± 3.5
	Post-test	1.24 ± 0.5 ***	1.42 ± 0.6 ***	11.8 ± 2.9 ***	0.88 ± 0.8 ***	2 ± 0 ***	10.3 ± 4.9 ***
	Post-test	1.79 ± 0.41 ***	1.92 ± 0.27 ***	15.7 ± 2.76 ***	1.74 ± 0.55 ***	2 ± 0 ***	15.7 ± 2.58 ***

* ($p < 0.05$), ** ($p < 0.01$) and *** ($p < 0.001$).

Table 4. The % effect of measured variables between pre-test and post-test.

Psycho-Pedagogical Parameters	Role Playing	The Expert Student	Vary the Ways Access to Information	Mind Map
Attention	50%	19.30%	235.13%	61.26%
Engagement	40.38%	5.15%	215.55%	38.13%
Return on error	43.09%	18.51%	89.37%	36.02%
Number of memorized keywords	80%	66.20%	175%	163.64%
Result of the written test	94.12%	57.01%	440.54%	181.69%
Satisfaction with the method by the students	32.19%	12.19%	49.13%	35.31%

The six psycho-pedagogical parameters of four neuro-pedagogical methods named “vary the access to information”, “mind map”, and “memory cards” vary in a highly significant way ($p < 0.001$) between the beginning and the end of each of the experiments at the level of the averages of the scores, going from 28.62% to 706.25%.

For the neuro-pedagogical method called “role playing”, there were variances of 80% for the number of key words memorized, 40.38% commitment, 50% for attention, 43.09% for the return on error, 32.19% for the satisfaction of the students towards the method, and 94.12% for the results of the written test (Figure 1).

Indeed, at the level of the averages of the attention scores, for the neuro-pedagogical method “vary the access to information” there is a significant increase of 235.13% $((1.24 - 0.37)/0.37) \times 100\%$ at the post-test compared to the pre-test corresponding to 0.37 ± 0.7 vs. 1.24 ± 0.5 . There is also a significant increase of 215.55% in active engagement, 89.37% in the number of words memorized, 175% in the error feedback, 440.54% in the satisfaction with the method and 32.19% in the written test (Figure 2).

For the neuro-pedagogical method called “the expert student”, there are variations of 66.20% for the number of key words memorized, 57.01% for commitment, 19.30% for attention, 18.51% for return on error, 12.19% for satisfaction of the students towards the method, and 28.62 for the results of the written test (Figure 3).

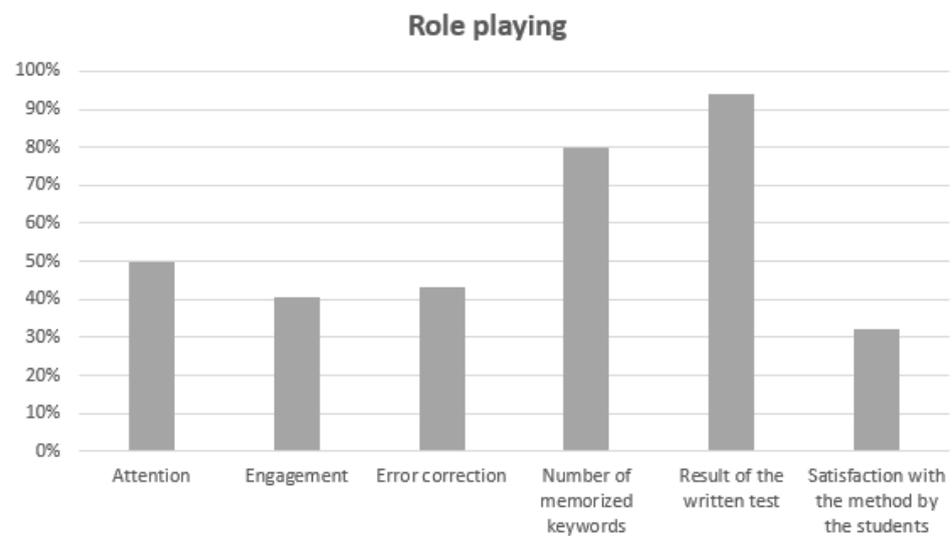


Figure 1. Percentage fields of the variations of the psycho-pedagogical parameters between the beginning and the end of the experiment in (%) for the “role play” method.

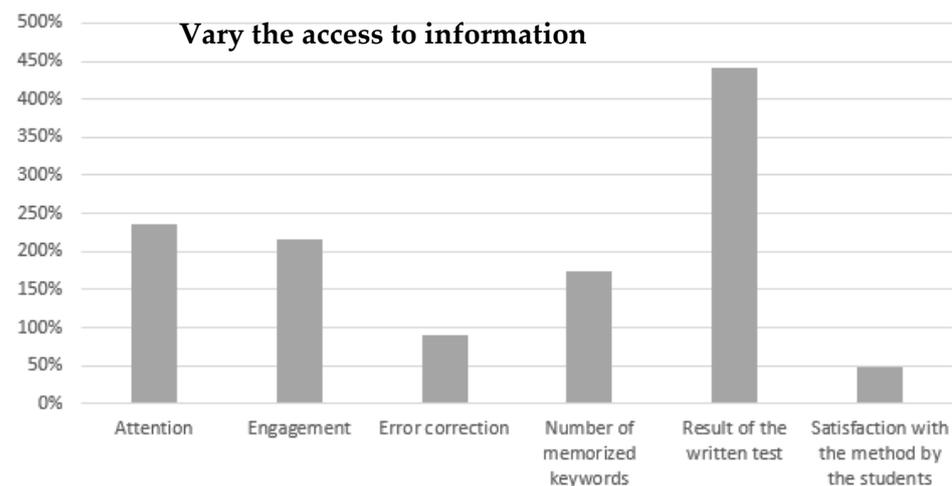


Figure 2. Percentage fields of variations in psycho-pedagogical parameters between the beginning and the end of the experiment in (%) for the method “vary the access to information”.

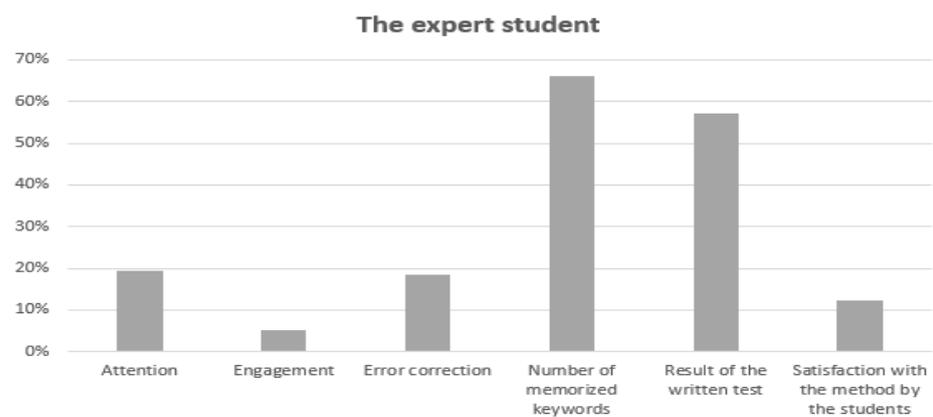


Figure 3. Percentage fields of the variations of the psycho-pedagogical parameters between the beginning and the end of the experiment in (%) for the “expert student” method.

Finally, the average scores of the “mind map” method, whose results are also highly significant, vary from 35.31% for the written test, 36.01% for the number of key words

memorized, 38% for active engagement, 61.26% for the parameters of attention, 163.63% for the parameters of return on error, and 181.69% for satisfaction of the students towards the method (Figure 4).

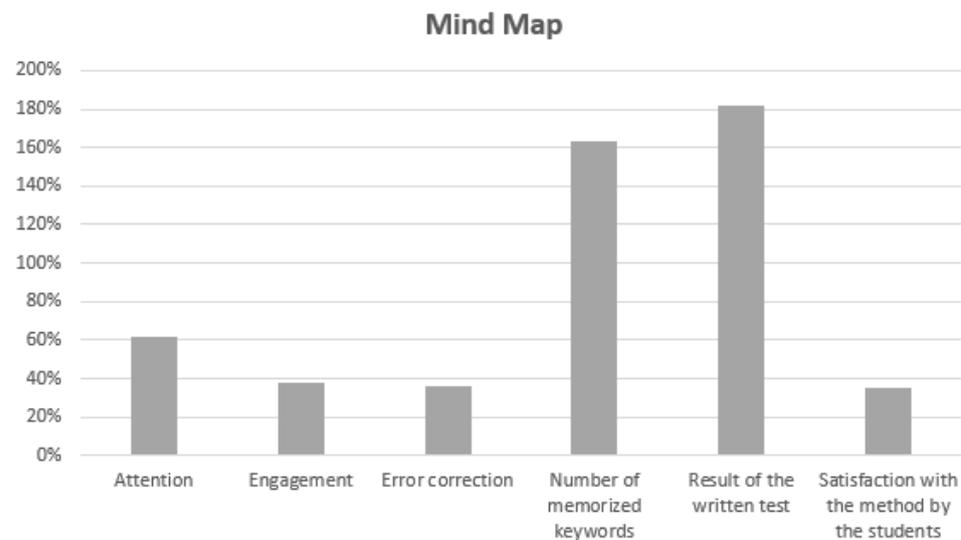


Figure 4. Percentage fields of variation of psycho-pedagogical parameters between the beginning and the end of the experiment in (%) for the “mind map” method.

It is easy to see from Figure 1 that for each treatment group, the relationship between post-test and pre-test is approximately linear. It is also clear that the linear relationship is similar for all three treatment groups, as illustrated by the simplified representation in Figure 5.

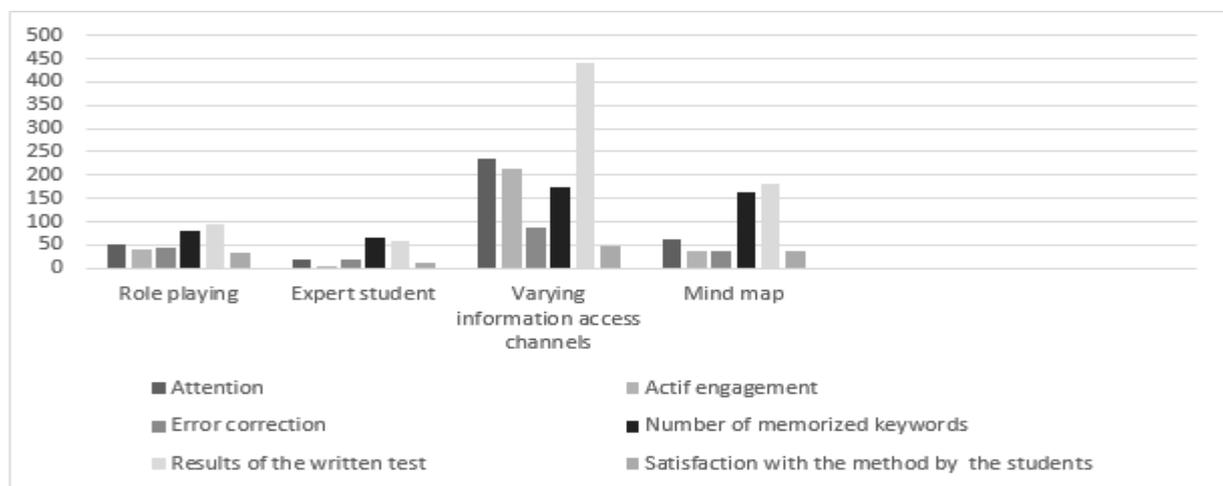


Figure 5. Percentage fields of the variations of the psycho-pedagogical parameters between the beginning and the end of the experiment in (%) for each of the neuro-pedagogical methods.

4. Discussion

Throughout this study, we have sought to highlight the effects of introducing neuro-educational data into the school and more specifically into classroom learning situations. The results obtained are promising.

For the neuro-pedagogical method “role playing”, a method designed to develop active engagement in students, our results show a significant increase ($p < 0.008$) of 40.38% in active engagement. Our hypothesis was based on our belief that role playing is action

learning [28]. It is “a fictional interaction in which one should participate by inventing a scenario and investing oneself in the skin of a character other than oneself” [29].

During this role playing session, students used analogies to represent the concepts studied; thus, learning is facilitated by comparing new information with known contexts [30]. This allows the internalization of concepts, and also explains the significant increase ($p < 0.05$) of 43.09% in the number of words memorized.

Reasoning by analogy is at the heart of the generalization and abstraction processes that allow the development of concepts and creativity and is one of the best strategies for explaining complex concepts [31]. It corresponds to the natural way in which the brain prioritizes information [32], allows the mind to convert known concepts into new knowledge, and plays an important role in deducing general representations from similarities, which in turn can be applied to solving new problems.

One of the reasons analogies work so well is that they take advantage of the brain's normal neural circuitry [33]. Despite the importance of reasoning by analogy for everyday life and in society, it remains fairly understudied [34]. The brain regions involved in analogical thinking are much less explored. Nevertheless, it has been found that certain types of analogical thinking activate the prefrontal and medial cortexes [35] and that the integrity of the left rostro-lateral prefrontal cortex is necessary in the processes related to reasoning by analogy. A study on this type of reasoning [36] concluded that the left posterolateral prefrontal cortex (with its long-range anatomical connections) is specifically critical for analogical reasoning and that a lesion of the left rostro-lateral prefrontal cortex may impair the relational integration and matching processes involved in abstract thinking. The critical bundles for analogy connect the frontal lobe to the temporal cortex (via the uncinate bundle), to the occipital cortex (via the inferior fronto-occipital bundle), and to subcortical structures [37].

Other areas are also mobilized during role play: the orbitofrontal cortex, mirror neurons, and Broca's field in the left hemisphere, which is associated with the empathy of the leader or group members. Particularly mobilized are the prefrontal cortex and limbic system of the protagonist who makes many connections, internalizes, judges, invokes memories, experiences, and perhaps restructurings [38]. Role playing is a technique where the player feels the emotional support of the group and the closeness they need [39].

For the neuro-pedagogical method “the expert student”, the students, firstly, must cooperatively build and produce explanatory presentations of the notions of the concept in their charge, and secondly, are placed in a competitive situation to present, in the best way they can, what they have produced in the cooperative phase. Our results show a significant improvement between the beginning and the end of the experiment ($p < 0.5$) of the psycho-pedagogical parameters, ranging from 19% to more than 66%.

At the neural level, cooperation provides a social incentive and is associated with an involvement of the orbitofrontal cortex, mobilization during such cooperation is considered closely related to the motivational control of target behaviors [40], and in the processing of positive feedback information [41]. This explains, in our opinion, the results recorded at the level of student engagement and their feedback on errors during this experiment; students developed an expert posture since each of them plays the role of the teacher and takes charge of the explanation of a concept for which they have become an expert, giving them a feeling of self-efficacy and acting as a central self-regulatory mechanism of human activity [42].

The active involvement of the students, with very limited teacher intervention during the experiment, improves the activity related to the cognitive task (e.g., working memory) [43]. This is perfectly consistent with our results, since the number of words memorized was significantly improved by 66.20%, and also allows the development of self-esteem and motivation which seem to modulate the neural activity related to learning. Self-determination theory [44] explains why students thrive when they are autonomously motivated, and it explains why they benefit when teachers support their autonomy. In-

dividuals with high self-esteem have greater volumes of gray matter in the right lateral prefrontal cortex [45].

The link is more subtle between emotional intelligence and metacognition [46]. Recall that the session in this experiment is conducted in two stages, the first of coordination and a second of competition which requires additional mentalization resources and is associated with an increase in medial prefrontal activity. The two positions of cooperation and competition lead to the activation of a common frontoparietal network subordinating the executive functions, (as well as the anterior insula, involved in autonomic excitation) [47].

The neuro-pedagogical method “Vary the ways in which information is accessed” speaks to how our brain is designed to capture simultaneously, in different modes, information received from the environment that is captured by the senses and sent by the nerves to the sensory regions of the brain such as the visual cortex, the auditory cortex, and the somato-sensory cortex. This offers a complementarity in perception, and a cross-reinforcement of information by multiplying access by exploiting the three indices: semantic, sensory, and emotional. It is by multiplying the access routes to stored knowledge that we facilitate its retrieval; learning occurs when two neurons communicate with each other, that is to say, when one neuron sends a message to another [48]. This information can then be used by the brain as feedback to adjust its neuronal connections. This action is important not only because it is essential for survival, but also because it allows the collection of new data about the environment and thus amplifies the effects of perception [49].

The results obtained from our experiment are in line with scientific findings on the differentiation of information access voices and their impact on students’ attention [50–52]. In fact, during this experiment, the attention of the students increased significantly ($p < 0.001$) by 253% and on the memorization, since the variation of the ways of accessing information allows the consolidation of knowledge, when an idea is evoked or a strategy is used, it is a set of neuron-neural networks that are activated together. Masson [13] thus responds to Hebb’s law “neurons that activate together connect together”, and in order to reinforce this connection to facilitate memory retrieval stimuli should be varied. The richer and more varied the stimulation of the senses, the more the connections are reinforced, if more than one sense is stimulated during learning, each recorded sensation then functions as a different input capable of leading to the totality of the information on a subject.

Our results also showed a highly significant ($p < 0.001$) improvement in memory between the pre-test and the post-test with a percentage of 175%; the richer and more varied the stimulation of the senses, the stronger the connections and the stronger the links between perceptual memory (senses) and episodic memory and the easier the retrieval of information [53].

The limitations of this technique are related to the lack of adequate material that allows this practice to achieve expected results, as well as to the effort that many teachers should make to better master its use. We propose that in the absence of didactic material, the teacher can be helped by software or open-source courseware and digital simulation resources that allow them to represent unobservable phenomena and to simulate physical interactions. The three-dimensional visualization illustrates in a simplified way a complex structure that can be manipulated in real time.

For the neuro-pedagogical method “Mind map”, studies conducted in different sectors such as design [54], medical sciences [55], linguistics [56,57], or economics and management [58,59] show that mind maps promote the structured representation of problems, memorization and creativity. The mind map is a graphic and playful way to represent ideas and to stimulate creativity [60,61]. The results obtained with this practice are in line with the vision of the above-mentioned authors. All the expectations were fulfilled, and the results show a highly significant increase ($p < 0.001$) of the psycho-pedagogical parameters, especially the results of writing and the number of memorized words, whose improvement reached 163.64% and 181.69%, respectively. Concept mapping can effectively function as an effective learning activity when it involves retrieval practice [62] because the use of mind mapping involves the linking of a word to prior knowledge which can allow for a

double coding of information in the verbal and visual components of long-term memory, thus allowing for more effective retrieval [63] since it this double coding involves increased neural activity in the left inferior prefrontal cortex. Increased activity in this region, regardless of the individual's intention to remember, leads to a more easily retrievable memory trace [64].

Concept maps cannot provide a solution for classrooms where rote learning predominates; but they do help, through the hierarchization of knowledge, to help students create meaning and reduce exogenous cognitive load, a kind of spatial contiguity which can promote a more semantically integrated understanding of the concept [65,66].

Cognitive function emerges from the hierarchical and embedded architecture of the nervous system [67]. One of the very important uses of concept maps is not only as a learning tool, but also an assessment tool, thus encouraging students, or teachers, to use meaningful ways of learning. The highly significant results ($p < 0.001$), 38.90% of the return on error, show that concept maps are equally effective in identifying correct ideas and incorrect ideas in learners [66,68,69]. Concept maps can be as effective as lengthy clinical interviews [70], since these tools involve both hemispheres of the brain: the left brain for language, logic, rationality and the right brain for imagination, creativity, global vision and analogy as well as the spatialization of information. It combines the use of these two hemispheres in perfect synergy [71].

5. Limits

Although our neuro-pedagogical methods have given satisfactory results, it is important to address certain limitations that will be dealt with later. Indeed, our methods are not yet validated by the scientific community, and our study is limited to a sample that does not include the primary and university cycles. It would also be wise to look at teaching and to take that into consideration because it is specifically limited to the teachers' feedback.

6. Conclusions

The contribution of neuroscience is extremely interesting. Learning has long been considered a cognitive phenomenon in the strongest sense; placed at the heart of "intelligence", it should be studied under its "functional" aspects and not exclusively under the behavioral angle. The results of our experimental research show a significant improvement of the learning parameters, for example, the exam marks which have improved from 57.01% to 440.54%. But it should not obscure all the other insights necessary for the pedagogical act, nor should it make teachers specialists (neuropsychologist, logopedist, orthopedagogue), or experts in the functioning of the nervous system, but rather help them to know how the brain processes information and what are the cognitive and metacognitive processes involved in the learning process. This will be the subject of our next article, in which we hope to accompany teachers in the introduction of cognitive neuroscience into the school world. This would be the launch of a beneficial opportunity insofar as it would make it possible to question and renew all practices, from the division of course sequences, their content, their rhythm, and the duration of their execution, to the objectives and the mode of evaluation.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to confidential reasons.

Conflicts of Interest: The authors declare no conflict of interest.

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