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Research report

Efficient learning produces spontaneous neural repetition suppression in prefrontal cortex

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ABSTRACT

Our study focuses on the physiological effects of repetition on learning and working memory using an adaptation of Luria's Memory Word-Task (LMWT). We assess the hemodynamic response in dorsolateral prefrontal cortex (DLPFC) of 13 healthy subjects while completing LMWT. Free word recalls were acquired at the beginning, middle and end of the task. Behavioral results showed that all subjects could recall the complete word list by the 10th trial, which was considered as successful task accomplishment. We observed an attenuation of stimulus-evoked neural activity in prefrontal neurons. Our findings show that the temporal integration of efficient verbal learning is mediated by a mechanism known as neural repetition suppression (NRS). This mechanism facilitates cortical deactivation in DLPFC once learning is successfully completed. This cortical reorganization is interpreted as a progressive optimization of neural responses to produce a more efficient use of neural circuits. NRS could be considered one of the natural mechanisms involved in the processes of memory learning.

1. Introduction

The capacity to learn and remember reflects the adaptive, plastic ability of the neural system to change in response to experience. Learning is the process of acquiring new information that leads to memorization when motivated information persists. Memory is a consequence of learning, a product of persistent functional and biochemical changes in the relationship between neurons. Learning is a change in the strength of precise neural circuits as a function of practice procedures. These neural changes are different from those produced by non-motivated training. Practice and repetition produce a restructuring – an anatomical shift – of functional activation in brain areas associated with the stimulus to be learned [1–3]. Practice as a learning process may modulate hemodynamic activity in the cerebral cortex, producing an increase, decrease or functional reorganization of brain activity [4,5].

Repetition is a natural learning method, refreshing information several times before it becomes permanently and temporarily accessible. When a stimulus is repeated, the neural activity produced with each repetition is normally reduced through a mechanism known as neural repetition suppression (NRS) (see Grill-Spector et al. [42] for a review). This mechanism may occur in different brain regions. The reduced level of hemodynamic changes associated with this repetition has also been reported in neuroimaging studies. We will use NRS to refer to decreased neural responses following stimulus repetition.

Learning by repetition requires repetition and the will to remember. It is a voluntary process. One cannot learn solely by means of a priming effect, which does not require the will to retain. What makes learning by repetition different is that the person's deliberate aim is to keep information in memory (working memory), temporarily or permanently. In learning by repetition, subjects are asked to maintain the repeated information in memory because they will have to report on it later. We define learning by repetition as the voluntary process of keeping information in memory, without deliberate manipulation, by means of periodic repetition. While repetition is a learning mechanism in and of itself, the voluntary cognitive effort that learning by repetition requires attention through motivation. According to Baddeley [6], learning by simple repetition is unlikely to succeed unless the learner plays an active part and puts some effort into the learning process (although with sufficient practice, the demand for attention becomes minimal). Motivation has a strong effect on learning. Attention to a stimulus is sufficient to cause its retrieval, whether or not the subject

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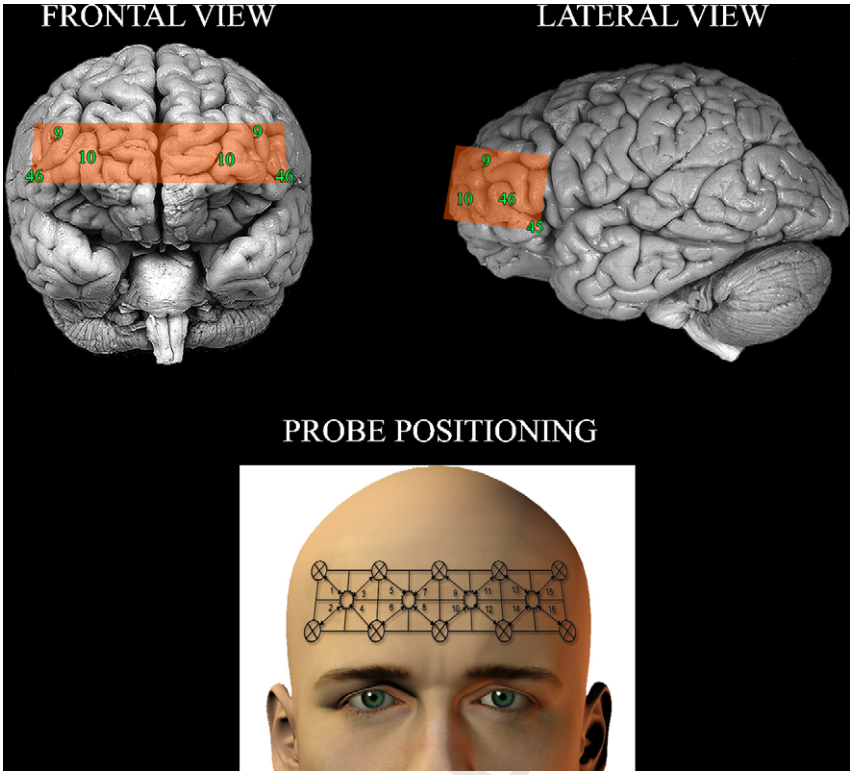

Fig. 1. (Bottom) image representing the fNIRS probe positioning in the human forehead. Four sources and 10 detectors configure a total of 16 information channels covering the whole probed surface. (Top) our fNIRS probe is designed to image DLPFC bilaterally [24]. Probed Brodmann areas include 9, 10 and 46.

intends to retrieve it [7,8]. Voluntary processes are intentional and controlled.

Different studies have demonstrated that functional hemodynamic changes occur after learning as neural activity in prefrontal cortex increases and decreases at specific times. However, the role of time in maintaining working information in the brain has yet to be determined. Prefrontal cortex (PFC) has been found to be part of the cortical network associated with practice and learning [9]. This cortical area has been linked to visual-motor [10,11] and verbal learning processes [1,2,12]. However, neuroimaging studies have been inconclusive in characterizing its role in these processes. Within PFC, the dorsolateral prefrontal cortex (DLPFC) has been associated with executive processes, namely working memory and maintenance of ongoing information. Working memory is the first temporal integrative function of PFC, playing a critical role in the temporal organization of learning [13–15]. Our previous studies have shown that the neural result of maintaining an arousing stimulus in working memory is a period of increased activation in DLPFC. This increase is not ongoing, since a decrease must occur at some point due to task achievement [15,16].

In our present study, we focus on the physiological effects of repetition on learning and working memory. We use an adaptation of Luria's Memory Word-Task (LMWT) to study functional hemodynamic changes related to learning by verbal repetition. Functional near infrared spectroscopy (fNIRS) is used to test the hypotheses that repeated verbal presentation of information will produce an increase in DLPFC activation only during learning, followed by a decrease in activation once the information has been learned.

In LMWT, a list of ten completely unrelated words is read aloud to the subject for he or she to memorize. This procedure is repeated ten times, while hemodynamic levels of oxyHb and deoxyHb are recorded. We compared the DLPFC hemodynamic activation pattern produced during a first period of word list learning by repetition, with that produced during a second period when the list was already learned but the words were still being repeated. In terms of haemoglobin concentrations, we hypothesize an increase in oxyHb and a decrease in deoxyHb in the DLPFC, reflecting activation of this area [17,18], during task learning phase, that is, when the subject is not yet able to recall the complete word list. Conversely, a significant drop in the regional-DLPFC oxyHb concentration, along with a significant increase in regional deoxyHb, is also expected, reflecting deactivation of our region of interest.

2. Materials and methods

2.1. Subjects

Thirteen healthy, right-handed volunteers (4 male and 9 female), ranging in age from 23 to 43 (mean 25.91, standard deviation 5.47), participated in the current study. IQ was estimated using the Barona method [19]; IQ averages were 117.13 for men and 115.37 for women. Written informed consent was obtained from all subjects. Protocol was in accordance with the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm) and approved by the Local Ethics Committee.

2.2. fNIRS description

fNIRS is an optical functional neuroimaging technique, developed according to the method designed by Chance and Leigh [20]. Both human [21–25] and animal studies [26–28] have tested the validity of this method. fNIRS is designed to detect changes in the concentration of haemoglobin molecules, the oxygen carrier of red corpuscles. The fNIRS light source emits a light that penetrates the brain. The proportion of light reflected by the corresponding molecules (i.e., oxygenated haemoglobin—oxyHb) and registered by the fNIRS detectors, determines how much oxygenated blood is present. Different studies have reported a high positive correlation between PET CBF measurements and fNIRS oxyHb, while a good spatial agreement has been found in studies that employed simultaneous fMRI and fNIRS (Kato et al., 2006; [29,30]).

Our fNIRS device (NIM, Inc., Philadelphia, PA) calculates relative changes to baseline values of oxygenated (oxyHb) and deoxygenated haemoglobin (deoxyHb) molecules by means of a continuous wave (CW) spectroscopy system, which applies light to tissue at constant amplitude. CW-type instruments rely on simplified assumptions regarding the tissue being probed and the changes occurring inside the sampling volume. Absolute concentration changes are very difficult to gauge

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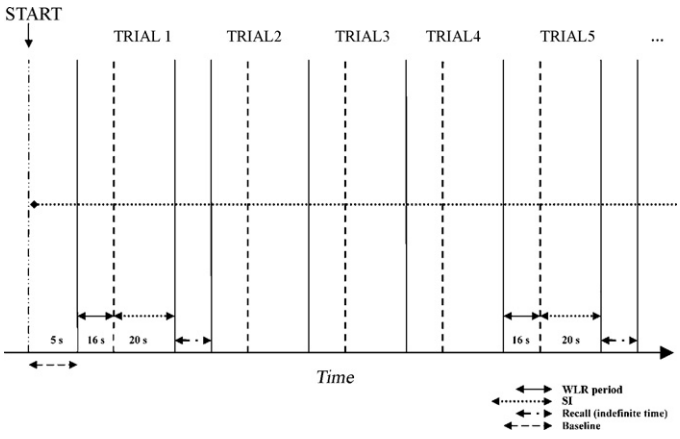

Fig. 2. Task completion and fNIRS data acquisition protocol. Firstly, a 5-s baseline is recorded. Then, subjects listens to the word list during approximately 16 s. This period is followed by a 20-s silence. Subjects then asked to recall the list in trials 1, 5 and 10. Recall period was not included in the statistical analysis. WLR: word reading period; SI: silence interval.

given that the real pathlength of light photons is unknown and cannot be measured or inferred.

The NIM probe is 17.5 cm long and 6.5 cm wide. It contains four light sources surrounded by ten detectors, for a total of 16 channels of data acquisition, covering an area of 14 cm × 3.5 cm on the forehead. A source–detector distance of 2.5 cm provides a penetration depth of 1.25 cm. The probe is positioned so that the line of sources is set at the line of fronto-polar electrodes [FP1–FP2] (in the International 10–20 system). This is designed to image cortical areas that correspond to DLPFC [24]. DLPFC generally occupies the upper and side regions of the frontal lobes. It is comprised of BA 9 and 46. Area 9 occupies the dorsal region of lateral PFC and extends medially to the paracingulate of humans. Area 46 is generally located at the anterior end of the middle frontal sulcus. The fronto-polar PFC, BA 10, is a region positioned above the Orbito Frontal Cortex (OFC), inferior to Area 9, and anterior to Area 46, serving as a junction point between the OFC and DLPFC (Krawczyk, 2002) (see Fig. 1). A complete data acquisition cycle lasts approximately 330 ms, making the temporal resolution approximately 3 Hz.

2.3. Assessment of verbal learning by repetition

Luriaĭs Memory Word Test (LMWT) [31], adapted and computerized by León-Carrión et al. ([32]; software available at www.neurobirds.com), is a measure with extensive clinical use which explores and assesses aspects of verbal memory and learning processes. It consists of a list of 10 words – read aloud to the subject with one-second intervals between each word – which the subject is asked to learn in ten consecutive trials. Subjects were informed that they had ten trials to complete this task and that the word list would be read at the beginning of each trial. The experimenter could not give feedback on the subject's performance during the course of the task.

Table 1
Mean oxyHb concentrations during the first and second halves of the test and statistical significance of the comparisons between them.

Channel	1st half (oxyHb)	2nd half	p
1	.038 (.023)	−.065 (.035)	.031*
2	.066 (.029)	−.064 (.035)	.012*
3	.045 (.019)	−.060 (.038)	.025*
4	.065 (.034)	−.059 (.045)	.018*
5	.063 (.040)	−.071 (.049)	.068
6	.053 (.035)	−.082 (.048)	.014*
7	.055 (.040)	−.059 (.052)	.120
8	.027 (.029)	−.080 (.044)	.021*
9	.028 (.044)	−.044 (.045)	.307
10	.009 (.043)	−.057 (.043)	.201
11	.029 (.053)	−.093 (.042)	.121
12	.011 (.042)	−.078 (.049)	.036*
13	.059 (.030)	−.079 (.039)	.041*
14	.055 (.040)	−.074 (.042)	.033*
15	.072 (.029)	−.072 (.037)	.012*
16	.027 (.038)	−.062 (.045)	.244

* Significant at 0.05 level.

Table 2
Mean deoxyHb concentrations during the first and second halves of the test and statistical significance of the comparisons between them.

Channel	1st half (deoxyHb)	2nd half	p
1	−.030 (.015)	.039 (.018)	.011*
2	−.035 (.018)	.043 (.017)	.006*
3	−.030 (.017)	.047 (.016)	.009*
4	−.008 (.011)	.028 (.014)	.041*
5	−.012 (.017)	.039 (.020)	.147
6	−.038 (.014)	.031 (.010)	.004*
7	−.040 (.014)	.055 (.032)	.016*
8	−.038 (.013)	.026 (.014)	.003*
9	−.060 (.018)	.055 (.029)	.008*
10	−.037 (.021)	.040 (.015)	.012*
11	−.037 (.022)	.025 (.013)	.033*
12	−.054 (.021)	.025 (.017)	.005*
13	−.049 (.015)	.042 (.017)	.000*
14	−.023 (.019)	.027 (.013)	.041*
15	−.043 (.027)	.050 (.020)	.030*
16	−.054 (.021)	.020 (.018)	.010*

* Significant at 0.05 level.

In the classic version of LMWT, subjects must recall the word list immediately after each word list reading. This test was adapted for our research purposes and recording settings: each word list reading (WLR) period was followed by a 20-s silence interval (SI) to allow the subject enough time to store the information. Subjects were informed that they would be asked to recall as many words as possible after certain trials, to assess the subject's level of engagement to the task. Our study

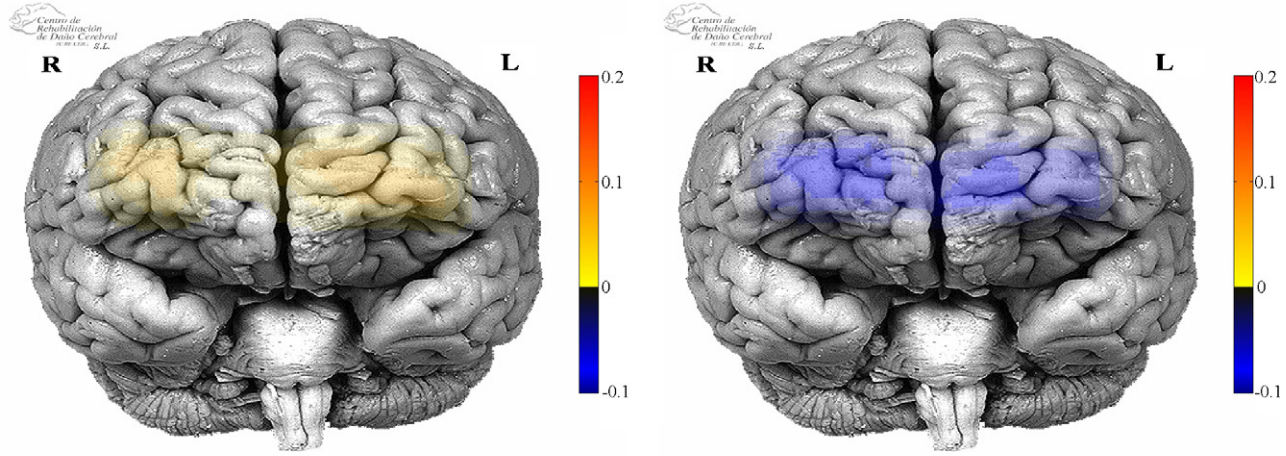

Fig. 3. Representation of oxyHb mean concentration for 1st and 2nd half of the test. In the 1st half of the test (left), the mean oxyHb concentration is over 0 in almost every area of DLPFC, showing a decrease below 0 in the 2nd half (right).

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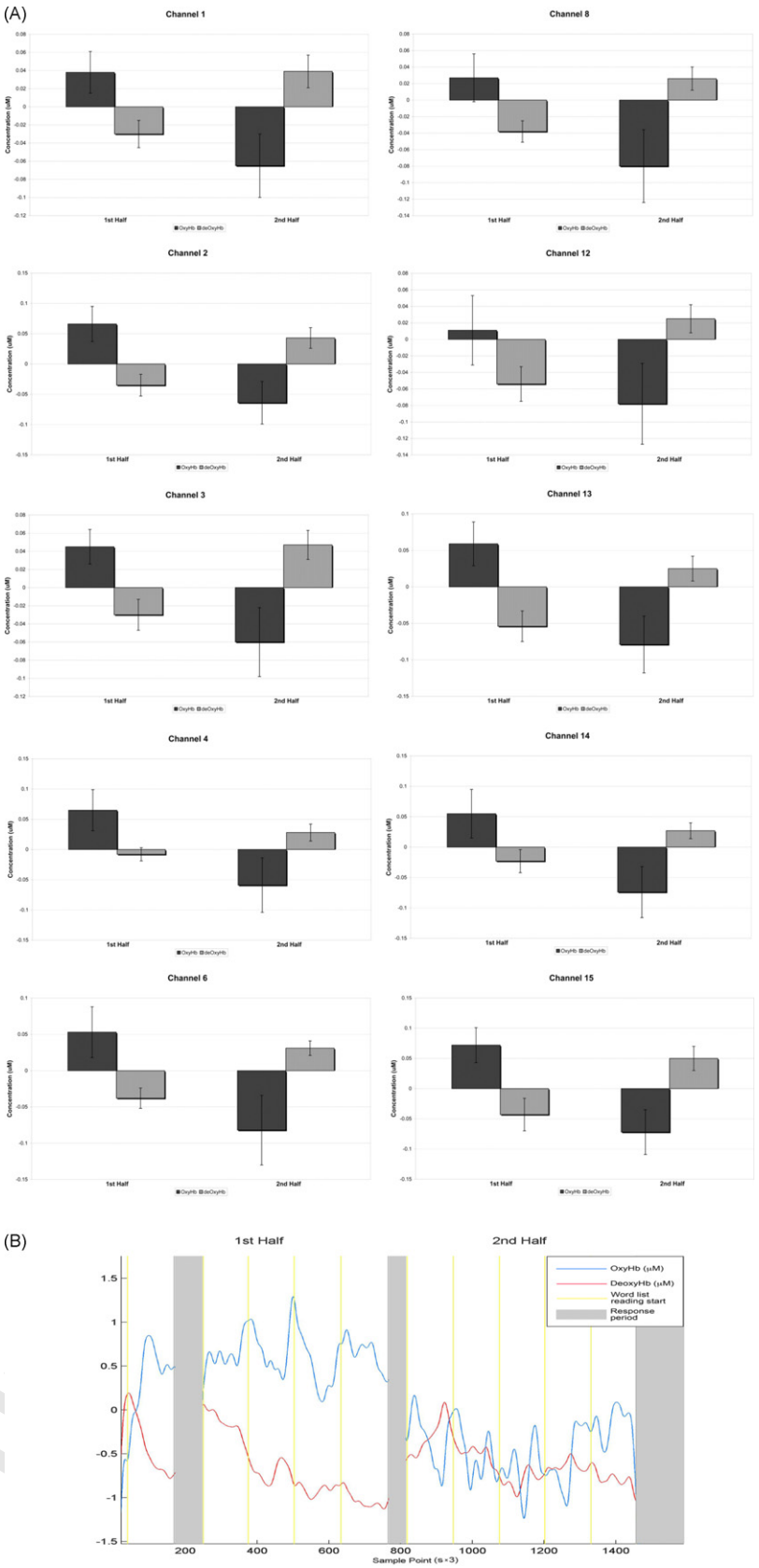

Fig. 4. (A) Bar graphs represent changes in the mean concentration of oxyHb and deoxyHb in each hemispheric prefrontal area (channels 1–4, 6 and 8 of the left DLPFC and channels 12–15 of right hemisphere) from the 1st half of the test to the 2nd half. A significant decrease in mean oxyHb and an increase in deoxyHb were obtained in all of these channels. (B) A typical time course of oxyHb (blue) and deoxyHb (red) changes across trials (subjects achieved recall of almost the complete word list in the 5th trial). Q3 Temporal course of the oxyHb is fluctuant but over 0 in the 1st half of the test, and below 0 when the word list is learned. The inverse pattern can be observed for deoxyHb. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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requested free-recall verbal answers only after the 1st, 5th and 10th trials. No feedback on the subject's performance was provided after these trials. In order to avoid deliberate learning in these trials, we did not inform the subject as to when the recall would be requested.

2.4. Experimental procedure

Sixteen-channel fNIRS data was collected from 13 subjects while they completed LMWT. The experimental protocol began with a 5-s baseline while subjects were resting. The experimenter then read the preset word list to the subject, which lasted approximately 16 s. This was followed by a 20-s silence. The list was then read again, or in trials 1, 5 and 10, the subject was asked to recall the words. He or she was given an indefinite period of time to do so, while the experimenter collected his or her answers (Fig. 2).

2.5. fNIRS data processing

We filtered the raw fNIRS data with a previously developed and adjusted finite impulse response low-pass filter (0.14–0.17 Hz) to eliminate possible heart pulsation, respiration artifacts, high frequency equipment noise, etc. [24].

Data on changes in oxyHb and deoxyHb relative to the initial 5-s baseline were calculated using modified Beer-Lambert law. In this study, we assumed a differential pathlength factor of 6, which is considered valid for measurements of the adult human brain [33]. We fit a first order quadratic polynomial to the oxyHb measurements and removed its contents from those recordings to eliminate possible low frequency signal drifts.

After epoch extraction, we performed baseline correction (normalization) by extracting the mean of 3 s of data prior to each epoch from the full epoch data which followed. Thus, we could observe hemodynamic changes related to the procedure of interest where its effects may be reduced and compare the differences in these changes among different procedures. The next step was to separate the first period of the test (trials 1–5) from the second (trials 6–10). The following step involved eliminating outliers by removing trials that generated epoch mean values 2.5 standard deviations away from each subject's grand average. After outlier elimination, trial averages for the first and second periods were calculated.

We deliberately omitted an analysis of the recall phase for various reasons: firstly, a free-recall verbal response has no time limit, making the analysis of inter-subject averages unsuitable. Secondly, given the modality of the response, the vocalization of the subject could produce artifacts in the signal. Only behavioral results were used to monitor the word list learning process.

2.6. Statistical analysis

Two 2-way ANOVAs for repeated measures (16 channels × 2 periods) were conducted. The dependent variables were oxyHb and deoxyHb concentration levels. Post hoc tests (Duncan's test) were performed to study the contribution of DLPFC regions to the processes here studied. Spearman's rank correlations were also calculated. We calculated the difference in words recalled in the first period (5th trial–1st trial) and correlated this variable with the difference in oxyHb concentration levels and the difference in deoxyHb levels for these trials. The same procedure was followed for the second period (10th trial–5th trial).

3. Results

3.1. Behavioral results

In trials 1, 5 and 10, we recorded all subject performances to assure that they had learned the complete word list. The percentage of subjects who recalled the complete word list varied across trials (Chi-Squared = 25.2; d.f. = 4; $p < 0.0001$). Only 7.69% (Adjusted residual [AR] = 1.4) recalled 10 words in the 1st trial, whereas 76.9% recalled the complete word list in the 5th trial. All subjects recalled the 10 words in the 10th trial.

3.2. Hemodynamic results

OxyHb results showed significant main effects of periods ($F[1,12] = 6.31$, $p = 0.027$). Post hoc analyses showed a higher level of oxyHb concentration during the first period of LMWT ($M = 0.044$ μM) than during the second ($M = -0.069$ μM) (Fig. 2). The remaining comparison and interaction did not reach significance (both p's > 0.9). DeoxyHb results showed a main effect of period ($F[1,12] = 20.68$, $p < 0.001$). Post hoc analysis showed a lower level of deoxyHb concentration during the first period of the test ($M = -0.037$ μM; corrected $p < 0.01$) than during the second ($M = 0.037$ μM) (Fig. 3). The remaining comparisons did not reach significance (all p's > 0.12).

Significant interactions between channels and period were also detected for oxyHb ($F[15,180] = 2.01$; $p = 0.016$) and deoxyHb ($F[15,180] = 1.81$; $p = 0.036$). Post Hoc analyses also showed that channels with significant highest differences between the first and second period of the test were 2, 3, 4, 13, 14, 15 and 16 (all p's < 0.05). These channels would correspond to BA 45, 46, 9 and 10 bilaterally. These channels also showed a lower deoxyHb concentration during the first period of the test (all p's < 0.05). Fig. 4 shows mean differences for significant channels between the two test periods, as well as typical temporal courses for oxyHb and deoxyHb. Tables 1 and 2 display these differences and associated statistical comparisons.

Correlation analyses showed significant positive correlations between oxyHb and memory performance in channels 1–4 and 12–16 for the first period (Spearmann's ρ's ranging from 0.54 to 0.73; p's ranging from 0.03 to 0.005). In these channels, significant negative correlations were found between memory performance and deoxyHb (ρ's ranging from −0.59 to −0.78; p's ranging from 0.02 to 0.003). For the second period, significant negative correlations were found between oxyHb and memory performance in channels 1–3 and 11–15 (ρ's ranging from −0.51 to −0.66; p's ranging from 0.04 to 0.013). Positive correlations between deoxyHb and memory performance were also detected for this period in channels 1–4 and 12–16 (ρ's ranging from 0.54 to 0.61; p's ranging from 0.03 to 0.014).

4. Discussion

We obtained one clear and significant result: during the learning process, an increase in activation takes place in right and left DLPFC, which then decreases or ceases when the learning is complete (Fig. 2). What we observed was the existence of Neural Repetition Suppression (NRS), defined as an attenuation of stimulus-evoked neural activity attributed to intrinsic and automatic processes in cortical neurons [34–36]. Our finding shows NRS in DLPFC after effective verbal learning, an adaptation of hemodynamic activity in DLPFC during multiple repetitions. The correlations between subject memory recall and fNIRS activation evidences the neurophysiological substrates related to LWMT (see Tables 1 and 2). The correlation analysis demonstrates memory performance during the first and second part of the task and associated hemodynamic activity in DLPFC. The physiological correlates of reduced memory load after repetition is NRS. Our data also reinforces the findings of Garrido et al. [37] that auditory learning is associated with repetition-dependent plasticity in the human brain.

In order to provide cognitive meaning to our results, we must first understand the biological significance behind the two different hemodynamic activities produced during the task: oxyHB increase and decrease. In a previous fNIRS study that sought to establish the relationships between prefrontal cortex (PFC) and cognitive control, we found that oxygen availability in superior PFC is linked to an increase in metabolism associated with attention level and effectiveness of cognitive control [16]. Matsui et al. [38] studied the hemodynamic response of the prefrontal area during words memory learning and found that during the task, oxyHb concentrations increased and deoxyHb concentrations decreased. Recently Molteni et al. [39] found that working memory load increased brain oxygenation during the first half of a memory task, which persisted throughout the central resting period. They also found that decreasing working memory load was coupled with oxyHb decrease.

An increase in oxygenation in right DLPFC during learning has been related to greater demands on cognitive control processes, with the goal of increasing neural and cognitive efficiency [40]. According to Büchel et al. [41], activation in specialized cortical areas changes with time during learning. Furthermore, the time

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course of these plastic changes is highly correlated to individual learning performance, reflecting the progressive optimization of neural responses elicited by the task. The psychobiological meaning of this finding is that NRS must be present in successful verbal learning to maximize the effectiveness and accuracy of learning, and also to free up space in working memory. This optimization of neural responses stems from a verbal learning process requiring time and repetition of the material to be learned to be effective.

Four mechanisms that may play a role in NRS were reported by Grill-Spector et al. [42]. Firing-rate adaptation, a sign of "reduced excitability", occurs briefly due to higher potassium currents that increase membrane conductance. Synaptic Depression, a short-lived drop in the efficiency of synaptic activity, is due to drops in "pre-synaptic neurotransmitter release". Long-term Depression, a sign of changes in plasticity due to "correlated pre- and post-synaptic activity", can last hours and tends to involve various stages (including protein synthesis). Finally, long-term potentiation, also long-lasting and involving various stages, is a sign of higher efficiency of synaptic activity. According to Baldeweg [43] and Friston [44], the effect of repetition supports evidence of a hierarchical sensory system that uses predictive coding, receiving bottom-up sensory input (evidence) from below and top-down input (prediction) from above. According to these authors, prediction error is reduced during stimulus repetition, producing an adjustment of the connection strength between levels through synaptic plasticity. The consequence of behavioral facilitation and reduced neural activity after stimulus repetition seems to be supported by long-term potentiation between neurons. The greater the number of repetitions, the faster and earlier memory trace processing is detected, diminishing hemodynamic response until no activation exists. This corresponds to the facilitation model proposed by Grill-Spector et al. [42] which assumes that synaptic potentiation causes faster processing and that facilitation will be more pronounced when top-down information is processed.

Decreases in extent or intensity of activation have also been found in studies related to task practice. Hebb [45] found that the ability to reproduce a short list of verbal items from memory improved immediately following presentation. This phenomenon, known as priming, has been studied to understand how prior exposure to a stimulus can facilitate its subsequent identification and classification. Priming is also mediated by repetition suppression and has been reported in imaging studies. Priming and memory by repetition are different processes. Priming does not require the same degree of encoding as does memory, occurring when an item is encoded and repeated. When a previously encoded item that reappears is neither the focus of attention, nor needed to complete the task at hand, its recent processing is not influential, as is the case in priming [35]. Some authors have found similarities between priming and the physiological properties of decreased neural responses occurring with item repetition. According to Sayala et al. [46] and Jansma et al. [47], the primary goal for underlying activation decreases is increased neural efficiency, and a more efficient use of specific 'neural circuits'. According to Poldrack [4], decreases in activation represent a contraction of the neural representation of the stimulus. While learning a task through practice, a decrease in the hemodynamic activity of DLPFC (such as we found) can reflect a good performance [47].

Our findings are consistent with the accepted evidence that DLPFC is highly involved in working memory. Active maintenance of information load in working memory recruits DLPFC [48–50]. We found higher bilateral levels of oxyHb in DLPFC during the learning process than during post-learning, suggesting that this region is involved in working memory. Working memory (WM) allows humans to maintain a limited amount of information in an active state for a brief period of time [51–53] facilitating efficient encoding of information [54]. The timely activation of neurons in PFC is crucial for efficient learning. Our data shows that effective learning by repetition produces a reduced demand on WM through decreased DLPFC oxygenation as a consequence of a shift from controlled to automatic processing. Our data is consistent with other behavioral studies reporting that practice of a cognitive task increases performance speed, reduces response variability, and lowers error rate. This reflects the transition from controlled to automatic processing. It also indicates that automatic and controlled processing have the same functional anatomical substrate, but differ in efficiency. According to Koch et al. [55], the transition from controlled to automatic processing WM is associated with exponential signal decreases in task-relevant regions, suggest that temporal changes in brain activation patterns can be attributed to enhanced efficiency of information processing as a result of cognitive practice.

Our finding of a NRS effect in DLPFC associated with verbal learning is a first among studies in the literature. Büchel et al. [41] suggested that a decrease in activation during learning enhances response selectivity through time-dependent changes in effective connectivity at synaptic levels. Our findings provide evidence that these decrements in DLPFC activation allow processing speed to increase and performance to improve [56].

In our study, we considered learning successful when all subjects (100%) could recall the complete word list. This occurred in the 10th trial. However, due to our experimental protocol and technique, we could not identify the trial where each subject had accomplished the task. Our behavioral data showed that the entire sample, as a homogenous group, accomplished the task in the last trial. LMWT is designed to assess clinical populations, particularly people with brain injury. Healthy subjects usually perform efficiently in this task, whereas learning rates are significantly worse in patients with memory difficulties [57]. Our data suggests that LMWT could be a valuable tool for memory assessment in patients with neurological damage.

In conclusion, our data also points out that NRS is necessary not only to complete or close learning, but to keep DLPFC free and available for engagement in other tasks upon demand. The NRS found in our study may be the first step in the temporal integration of learning; first the representation of new information is maintained in DLPFC during learning; then it is stored in a more permanent place for future use. NRS seems to be a natural physiological phenomenon that occurs when an the repetition of an item is motivated, regardless of its behavioral significance This is an important finding for educational purposes, as it reinforces the psychobiological role of repetition in learning. Our results also have implications for serial studies using neuroimaging and for treatment of memory disorders in patients with acquired brain injury, but further studies are needed in this regard.

Uncited references

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[58–60].

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