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Phase synchronization of oxygenation waves in the frontal areas of children with attention-deficit hyperactivity disorder detected by optical diffusion spectroscopy correlates with medication[1]

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Phase synchronization of oxygenation waves in the frontal areas of children with attention-deficit hyperactivity disorder detected by optical diffusion spectroscopy correlates with medication

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Abstract. The beneficial effects of pharmacotherapy on children with attention-deficit hyperactivity disorder (ADHD) are well documented. We use near-infrared spectroscopy (NIRS) methodology to determine reorganization of brain neurovascular properties following the medication treatment. Twenty-six children with ADHD (ages six through 12) participated in a modified laboratory school protocol to monitor treatment response with lisdexamfetamine dimesylate (LDX; Vyvanse®, Shire US Inc.). All children refrained from taking medication for at least two weeks (washout period). To detect neurovascular reorganization, we measured changes in synchronization of oxy (HbO_2) and deoxy (HHb) hemoglobin waves between the two frontal lobes. Participants without medication displayed average baseline HbO_2 phase difference at about −7-deg. and HHb differences at about 240-deg.. This phase synchronization index changed after pharmacological intervention. Medication induced an average phase changes of HbO_2 after first medication to 280-deg. and after medication optimization to 242-deg.. Instead first medication changed of the average HHb phase difference at 186-deg. and then after medication optimization to 120-deg. In agreement with findings of White et al., and Varela et al., we associated the phase synchronization differences of brain hemodynamics in children with ADHD with lobe specific hemodynamic reorganization of HbO_2- and HHB oscillations following medication status. [DOI: 10.1117/1.JBO.17.12.127002]

Keywords: attention-deficit hyperactivity disorder; brain imaging; near-infrared spectroscopy; children; medication; naïve.

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1 Introduction

Problems of attention and hyperactivity in the child's behavior can be successfully regulated with medication therapy.[1] The physiological mechanisms underlying stimulant medication treatment effects have been well characterized.[2–4] However, the mechanisms involved in the cortical-neurovascular response to pharmacological treatment are not as well understood.

It is known that during rest the brain shows high levels of spontaneous activation; this status of activity is called the rest-state. Many studies have measured brain activation during rest-state demonstrating that different smaller brain regions and larger brain areas have a nonstop active connectivity which is indicative of anatomical pathways of inter-regional communication.[5] Research has been consistent in showing a number of rest-state networks that are active in the brain. Among these the default-mode-network links the brain medial region and the bilateral inferior frontal regions with the posterior cingulated cortex. Results in van de Heuvel et al.[5] support the idea that different regions of the default-mode network are active regions connected via anatomical white matter inter-hemispheric tracts, the cingulum tract, the left and right superior frontal-occipital fasciculus and the genu of the corpus callosum.

The default-mode brain network is responsible for fundamental cognitive processing including attention and has been studied in children with attention deficit-hyperactivity disorder (ADHD).[6,7] Research has shown that the brain activation occurring in designated default-mode-networks, maps onto dopamine and attention pathways.[7] In addition, default brain areas that are active during rest states are thought to be predictive of active areas due to specific cognitive tasks.[7–9] The present study aims to identify rest-state oscillatory features of brain oxygenation in the right and left frontal cortex in children with a diagnosis of ADHD. The purpose of the protocol was to study connectivity of the left and right frontal cortex of the default-mode-network relevant in children with attention problems and using a known factor of activation and reduced/optimized activation, psycho stimulant prodrug LDX. We used the frequency domain near-infrared spectroscopy (NIRS) method to measure the brain hemodynamic variations in the frontal areas of six to 12-year-old children with ADHD with no previous medication treatment for their behavioral symptoms. Phase synchronization of the oscillatory change of oxy- and deoxy-hemoglobin

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(HbO_2, HHb, respectively) in the brain was our primary study parameter. Phase synchronization is a traditional concept in physics. It has been studied with electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).[10–14] Phase is used here according to what Rosenblum and colleagues[15] proposed in the literature and in agreement with recent concepts of brain modes of reciprocal integration.[13] In the present study, the phase is characteristic of the patterns of oscillations of HbO_2 and HHb between the left and right frontal cortex. Since we are interested in the synchronization of the waves but not on their amplitude, we employed the synchronization index previously introduced that is insensitive to the amplitude and frequency of the waves. This approach offers major advantages, capturing the probability distribution of phase synchronizations and their distribution peak.[16,17] Based on this approach, we constructed a quantifiable index of phase synchronicity and its distribution. The parameters of this distribution are indicative of cortico-cortical mechanisms of coordinated flow between brain areas due to cortical activation and oxygen metabolism occurring at different spatial locations.

It is hypothesized that stimulant medication as an intervention induces a reorganization of the local neurovascular recruitment and influences local metabolism by changing the peak phase synchronization value following the peak of pharmacodynamic efficacy. We had no specific prediction of the direction of the phase that the brain reorganization would take because this is a new area of investigation. For instance, different networks of brain activate independently, yet they may overlap by means of communicating with one another via hemoglobin oscillations that travel across the brain. It is our intent to examine this inter-independency in light of reciprocal neurovascular connections occurring between areas at the same level in the network according to mechanisms of integration of information.[9,13,17]

In the past 60 years, medication therapy has been the first line choice to treat those with ADHD. The effects of ADHD on behavior and school performance are well established and the effects of medication are very powerful.[18] The relationship between the brain and amphetamine-derived medication, however, is controversial for two reasons. The brain pathophysiology of ADHD is controversial because it is difficult to identify theories of brain differences that agree. Medication therapy using amphetamines is controversial because, although they enhance attention and wakefulness acting selectively on those brain neurotransmitters (dopamine, serotonin, and norepinephrine) that are specifically involved in executive functions, their mechanism of action is subject to misuse and dependence.

Lisdexamfetamme dimesylate (LDX) is perhaps the most common amphetamine prodrug for the treatment of symptoms of ADHD. The concept of prodrug refers to the formulation of the drug that allows extended pharmocodynamic properties. In brief, the prodrug formulation alters the pshysiochemical properties of the drug that remains inactive until metabolized into an active form, *d*-amphetamin.[18]

The conversion of LDX into active *d*-amphetamine occurs mainly in the blood. The effects of medication can be very powerful. Two main reasons address the relationship between brain and amphetamine-derived medication:

(1) The brain pathophysiology of ADHD is controversial because it is difficult to identify theories that agree in identifying brain differences; and

(2) pharmacotherapy using amphetamines is controversial because, although they enhance attention and wakefulness acting selectively on brain neurotransmitters involved in executive functions, their mechanism of action is subject to misuse and dependence.

The clinical success of LDX is due to the benefits of its formulation, extended duration, and consistent effects during the day and reduced potential for abuse. Also LDX is used and studied for its potential benefits on the dopaminergic pathway that is involved in the inattentiveness, impulsivity and hyperactivity observed in those with ADHD.

Once administered, the first response to LDX can be observed in the same day within a few hours; in less than a week the effects to the first and lower dose (30 mg minimum dose) are clear after which, if necessary, dose can be adjusted (70 mg maximum dose). In four weeks the effects are established, meaning they reached optimal behavioral response from the baseline visit, meaning the benefits significantly outweigh the medication side effects. In fact, the dose adjustment is decided carefully balancing positive behavioral effects and adverse events relying on expert clinical judgment. This decision is a combination of qualitative and quantitative evaluation of the individual response to medication using standard scales and the clinician's specific expertise in the field of ADHD.

2 Materials and Methods

2.1 *Laboratory School Model*

This was a single-blind modified laboratory school protocol study[19] providing a highly controlled experimental setting to monitor time sensitive medication effects of LDX on brain hemodynamics in children aged six to 12 years. The study protocol was approved by the University of California (UC), Irvine local institutional review board as well as by the State Research Advisory Panel of California. This study was conducted in the same sample in which we investigated symptoms of inattention and hyperactivity/impulsivity and reading performance as well as cardiovascular parameters in response to stimulant treatment, respectively.[19–21] Although the complete subject demographics are presented elsewhere,[19] the breakdown of subjects by ADHD subtype are as follows: six (23%) predominantly inattentive; predominantly hyperactive-impulsive: zero (0%); and 20 (77%) combined subtype. A total of 28 children diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR)[22] were recruited for this study. Of the original sample, 26 participants (six females and 20 males) completed the NIRS study. In addition to meeting DSM-IV TR criteria, we screened each participant for previous medical history, and clinician evaluation included a Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) present and lifetime versions[23] and an ADHD-Rating Scale-Version IV completed at baseline with a score ≥ 1.5 SD above the norm.[24] Other inclusion criteria included age appropriate intellectual functioning by IQ score ≥ 80, and blood pressure within the 95th percentile for age, gender and height. To qualify for participation in this study, the children had to show a severity score > 30 on the ADHD Rating-Scale-Version IV (ADHD-RS-IV).[24] Additional clinical presentation of these participants as related to cardiovascular parameters and adverse events are already available.[20,21]

A detailed diagram of the study visits and design is depicted in Fig. 1. The phases of the study included screening followed by an extended Baseline visit in which subjects were measured on clinical scales and NIRS prior to initiation of LDX dose and again at 2 to 4 h post-dose, a time of expected peak efficacy based on prior studies.[25,26] Licensed medical staff administered the LDX treatment on site to ensure exact timing as is typical in the highly structured and standardized laboratory school protocols. Four to five weeks of open-label, stepwise dose optimization with weekly ADHD symptom assessments followed the Baseline visit. Finally at three to four weeks from the first medication exposure, children participated in an extended half-day modified laboratory school visit. This visit was single-blind to capture behavioral and changes in NIRS measurements due to medication effects at optimal dose. Optimal dose refers to the dose that produced a significant reduction in the symptoms of ADHD observed using the ADHD-RS-IV and Clinical Global Impression[24,27] scores.

2.2 *Optical Instrumentation*

Optical measurement was performed using a frequency domain near- infrared spectrometer (Oximeter; ISS, Inc., Champaign, Illinois), at two wavelengths (830 and 690 nm), 110 MHz intensity modulation frequency. The instrument brings light to the tissue and collects it on the surface through sixteen laser diodes sources, eight per wavelength linearly multiplexed, and two photomultiplier tubes (PMTs) as the optical detectors.[28,29] Acquisition frequency was 9.75 Hz.

Light in the spectral range of 690 to 830 nm is sensitive to the absorption of oxygenated and deoxygenated hemoglobin, HbO_2 and HHb, respectively. In the near infrared spectral range HHb and HbO_2 are the main absorbing chromophores in biological tissue and the peak of their absorption spectra is different (Fig. 2), hence we can separately determine their concentrations according to the specific extinction coefficient for the selected wavelength.[28–31] At a wavelength of 690 nm, light absorption by HHb is significantly larger than absorption HbO_2, while for a wavelength of 830 nm the HbO_2 absorption is significantly higher than HHb absorption (Fig. 2). We used a dual optical sensor to probe the left and right frontal areas simultaneously. The probe was placed on the participant's forehead (Fig. 3). Each sensor is symmetrically designed with four pairs of light sources and a photon-multiplier-tube (PMT) detector. The source-detector distances are arranged in a linear way at distances ranging from 2.00 to 3.56 cm from the PMT and half a cm apart from each other. Each laser fiber shed light at one wavelength (at 830 and at 690 nm), to create a spot of light

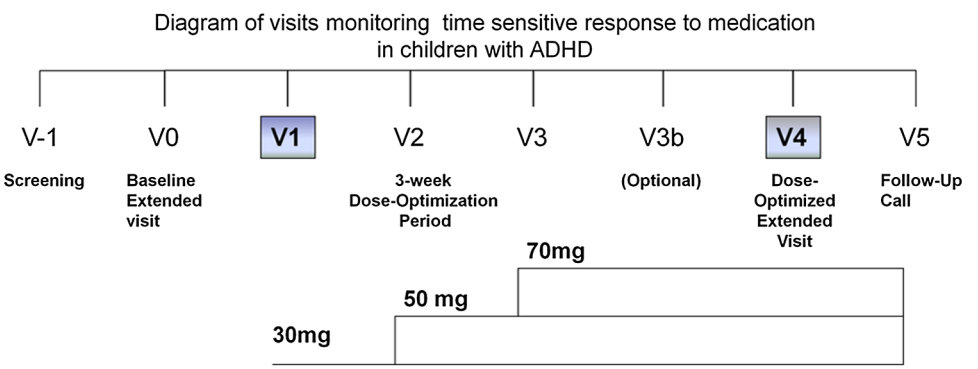

Fig. 1 Diagram representing the study design. At V1 patient were first exposed to medication, at visit 2 they increased up to 70 mg; at V4 they reached dose optimization.

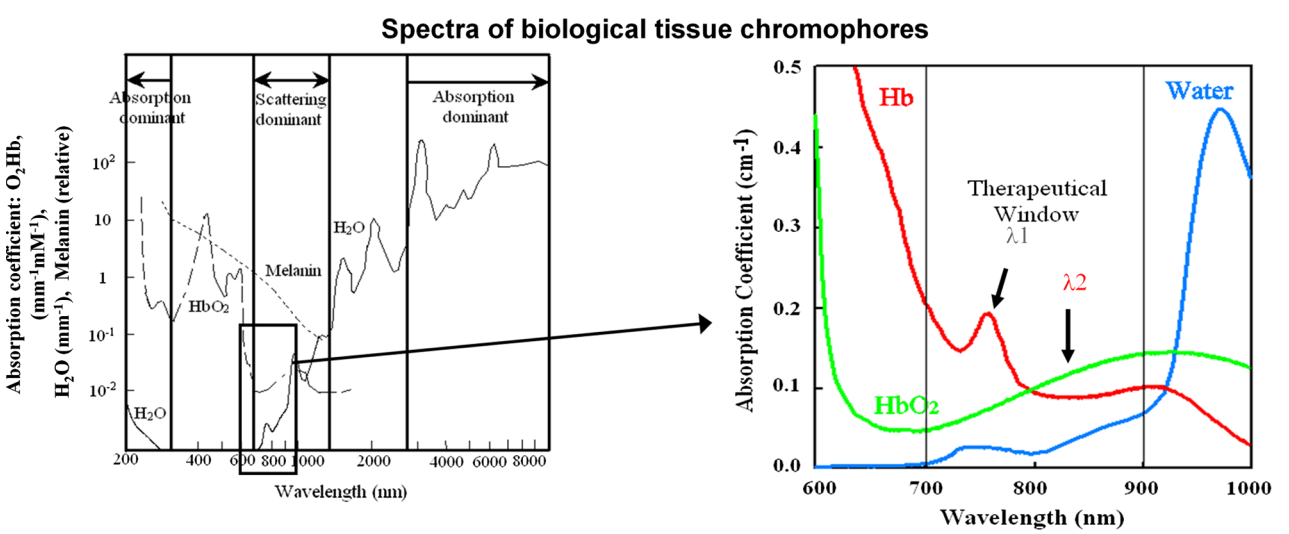

Fig. 2 An example of NIR spectral window when measuring biological tissues. Within the therapeutical window, wavelength specific sensitivity to oxy- and deoxyhemoglobin are measured and optical properties of absorption and scattering are quantified.

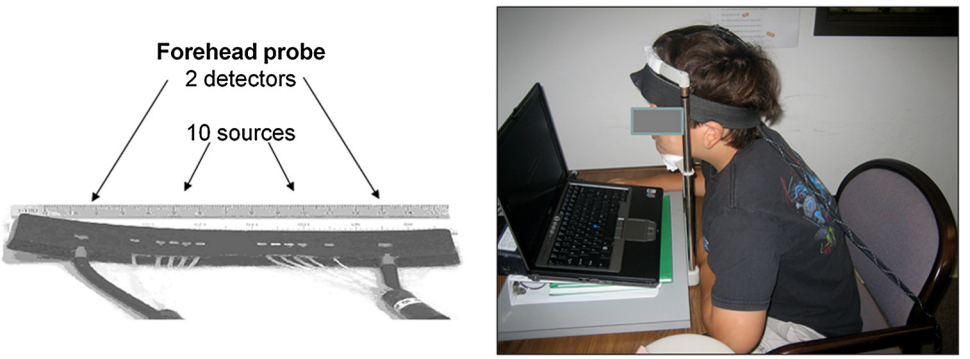

Fig. 3 Picture depicting a participant wearing the NIRS probe during a session.

on the tissue measuring both chromophores in the spectrum. Two light collecting fibers, one for each wavelength are inserted in an ergonomic sterilizable silicon band and coupled to a prism. Light shone at these distances penetrates about 1.5 cm in the head as a function of distance from the PMT, measuring changes on the first 2 mm of grey matter on the brain, an area rich with arterioles and venules.[30,31] In this study we used the 4-distance method to obtain a single value of HbO_2 and HHb, according to the multi-distance protocol described in the literature.[32,33] The multi-distance frequency domain method is quite immune from the "skin" artifacts since the changes due to skin contact and skin blood flow are common to all four distances. In addition, the system is calibrated before each measurement session to check for long terms drift of the instrumentation.

2.3 *Optical Data Analysis of Phase Synchronization*

The determination of the phase synchronization between the oscillations of two time series was performed using the Hilbert transform method. We compared time series of HbO_2 and HHb measured in the left and right frontal areas. The Hilbert transform method was originally conceived to determine synchronization between the pulse, the breathing rhythms and brain activity.[34–36] The mathematics of the method was previously described in the context of near-infrared spectroscopy.[36] In brief, the method uses the discrete Hilbert transform to calculate the most probable phase delay between two time series. The entire time series is divided in segments of about 20 to 30 s, and for each segment a value of the phase between the two series is calculated. A histogram of the values of the phases so obtained represents the probability density function of two time series being synchronized. From this histogram, a phase synchronization index (PSI) is calculated that statistically indicates the average phase between the two signals and the variance during the entire run. We can mathematically detect the behavior of the phase based on the maximal deviation from a uniform distribution. Therefore we can obtain phase locking strength if interacting oscillators are quasi-linear by comparing their relative phase distribution with a uniform distribution. This method, called "phase binning" allows the comparison of the distribution of phase synchronization in time series samples.

The PSI quantifies how much the phase-locked distribution is different from a uniform distribution. This quantification is associated with the probability of phase difference. We can calculate the width of the probability distribution and characterize it as a conditional probability function for two oscillators ϕ_1, ϕ_2:

$$\eta = \phi_2 \bmod 2\pi n|_{\phi_2 \bmod 2\pi m = \vartheta}, \tag{1}$$

where n is an integer. If the oscillators are not synchronized, η should be uniformly distributed in the interval, otherwise it will cluster around a value (we assume unimodal distribution). To quantify this distribution the algorithm calculates the dispersion of the data points over a defined interval of time. Since each interval of time is divided into N bins, it is necessary to calculate the probability that certain values belong to each bin:

$$\Lambda_\lambda = M_l^{-1} \sum_{i=1}^{Ml} \exp\left[i\left(\frac{\eta_{i,l}}{n}\right)\right], \tag{2}$$

where M_l is the number of time intervals. To improve the statistics, the phases are averaged over all N bins providing the synchronization index:

$$\lambda_{n,m} = N^{-1} \sum_{l=1}^{N} |\Lambda_l|, \tag{3}$$

where n and m are the number of time intervals and the number of bins, respectively. These calculations were performed by the BoxyRead program Software (available online to download upon request by *E.* Gratton: www.lfd.uci.edu). Data filtering procedures applied a low pass IIR filter (0.8) filter and a high pass filter with linear detrending to the time series of HbO_2 and HHb to decrease the effects of rhythms. This procedure avoids detection of artificial phase-synchronization due to obvious rhythms (heart beat and breathing frequency) that are common in both time series. In practice, due to the requirement that a power of 2 of the data points are used to take advantage of the computational speed of the Fast Fourier Transform algorithm, the Hilbert transform was calculated over 32 points in the time series (1 child at 64 points to compensate a difference in the acquisition rate). The final computation provides summary statistics of the phase-synchronization histograms. The average PSI was 0.44 for all trials and was never below 0.4. This is considered a relatively high value for the PSI.

3 Results

Figure 4(a) and 4(b) shows histograms of the phase-synchronization index for all participants before (red), after first medication (blue) and after optimization of the medication (green). In this figure, the phase data are binned in eight regions of 45 deg width. This complete data set in Fig. 4(a) and 4(b) shows underlying commonalities between participants. For each trace in

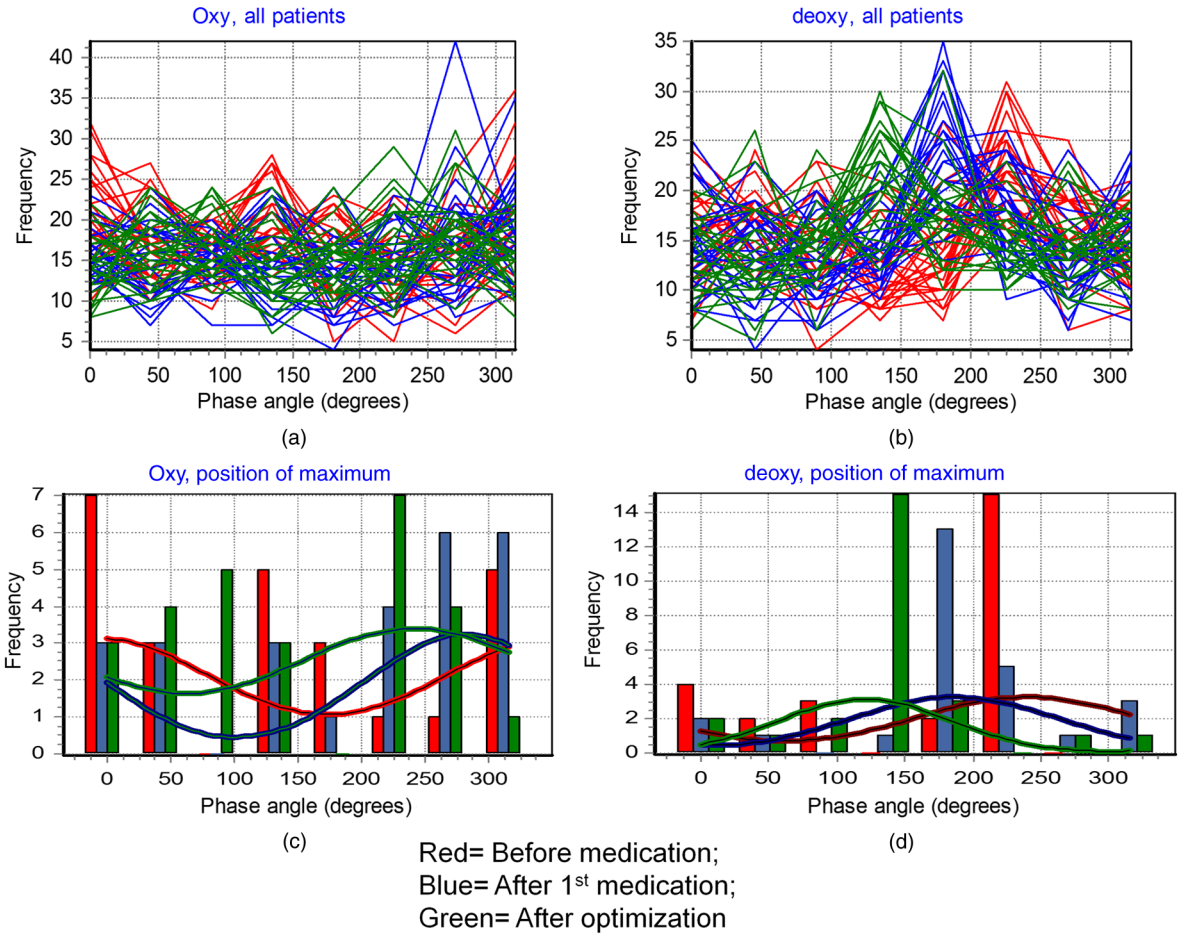

Fig. 4 Histogram of phase synchronization for all subjects. For the histograms the phase angle has been binned in interval of 45 deg. (a) Phase synchronization of oxyhemoglobin. Individual traces are color coded according to the legend. (b) Phase synchronization for deoxyhemoglobin. (c and d) Histogram of the angle maximum for each trace of part (a) and (b), respectively. Solid curves are Gaussians with center and standard deviation obtained from the central moments of the histograms. Data are wrapped around 360 deg.

Fig. 4(a) and 4(b), we determine the angle of the maximum. In Fig. 4(c) and 4(d), we report the histogram of the trace maximum for all participants, coded in color according to the legend in Fig. 4. For each histogram, we calculated the center and the standard deviation and draw a line in the histogram plot corresponding to the Gaussian with a given center and standard deviation [solid lines in Fig. 4(c) and 4(d)]. In Fig. 5, we show a clear trend for the evolution of the average phase for each of the three conditions (before, after 1st medication, and after optimization) for the oxy and the deoxy phase synchronization. The center identifies the most probable phase vector distribution. The black bars on each symbol correspond to the standard deviation of the histograms.

4 Discussion

The concept of phase syncronization has been applied to different techniques to study and image the human brain,[37] and researchers have successfully identified phase coherence, reset, shifts, and lock periods as physiologically generated and functionally related to a reciprocal network of brain areas relevant to the brain rest-state.[36,38–40] We report here the phase difference between the frontal lobes in three different conditions, before medication, after 1st medication, and after optimization. We also report the phase change for each participant induced by medication. Most of the participants had their HHb phase synchronization values clustered in a relatively narrow distribution [Fig. 4(d)]. Instead the participant's HbO_2 average phase synchronization values were less clustered under all conditions.

In the results for the phase histogram of the number of children with ADHD, the experimental session was the main factor with a phase group average changes of more than 90-deg.

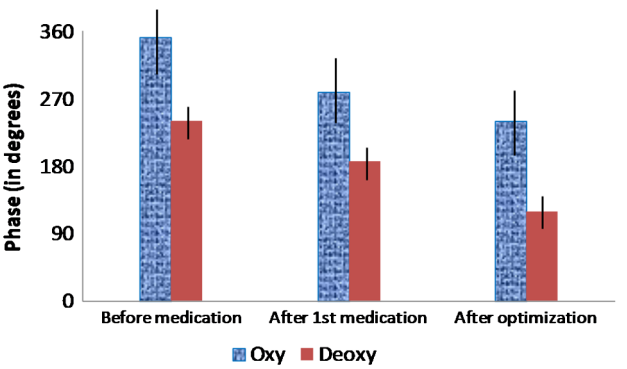

Fig. 5 Center and standard deviation (black lines above each bar) of the histograms of Fig. 4(c) and 4(d), for the synchronization of oxy and deoxyhemoglobin, respectively. A paired *t*-test and *p*-values calculation for the comparison of after 1st medication and after optimization with respect to before medication gives values in the range $p < 0.0001$ using the averages and standard deviation obtained from the data of Fig. 4.

(Fig. 5). This result suggest that the average phase change is sensitive to different volume of brain tissue sampled due to reactivity to local regulation of low-frequency hemodynamic fluctuations from the right and left frontal brain regions.[38]

The overall phase change is in the direction of the phase value observed in normal subjects. The observed phase change was proportional to dose and time-effects of medication. Although the protocol does not allow distinguishing these effects in a scaling way, the protocol confirms a gradual decrease of phase as dose is introduced. There was an initial phase decrease at first drug exposure (of at least 30 mg), another occurred at dose optimization (>30 mg <70 mg). Thus, it appears that the phase synchronization changes in a linear way with the increased medication dose.[41]

In our measurements, the phase synchronization of HHb changes of about 80 deg, or less, on the quadrature (Fig. 5) at the time of medication first exposure and after four weeks at dose optimization. The phase synchronization changes are in the same direction for O_2Hb, but over a slightly different range of values.

The catecholaminergic model explains features of ADHD based on the process of facilitation of synaptic reuptake of dopamine; in turn *d*-amphetamine can activate neurovascular events. These effects can be twofold: the dopamine release and reuptake are associated to improved symptoms of ADHD; neurons become more susceptible to the activation of the brain reward pathway that modulates seeking behavior, a behavior associated to misuse of substance.

In this research design, the same individuals were their own controls. Future research could benefit from further compassion measure using a stimulant medication of the methylphenidate family, evaluating different doses over several multiple time-point measurements, and adding a larger number of brain regions and conditions.

The phase synchronization of brain hemodynamics in the frontal areas is suggested to occur through a mechanism of reorganization of reciprocal oxygen metabolism.[39,40] Using NIRS measurement performed in children with ADHD, we observed that rest-state hemoglobin fluctuations are locally regulated in the frontal brain areas. Specifically, our results of phase synchronization point to a defined physiological and mental state[42,43] that deals with effort and a mechanism of oxygen recruitment. This is in agreement with the idea of networks of active brain areas during rest in those with attention problems.[44,45] The innovative aspect of our study is in the methodological approach that integrated Hilbert transform of hemoglobin phase synchronization between different cortices to detect medication effects that occur over time and that have physiological effects with unknown long-term effects on brain tissue resiliency. We were able to identify difference in phase shift direction between oxygenation waves in the frontal lobes before and after medication. This is an unprecedented result for brain hemodynamics in children with ADHD since it informs us of the non-stationary, nonlinear nature of the brain physiological regulation in response to medication therapy that ameliorates symptoms of ADHD and improves reading performance.[20] The observation that the brain hemodynamic changes in response to pharmacological intervention are expressed as phase shifts of HbO_2 and HHb between the left and right frontal areas, and that larger changes are required to HHb, describes a mechanism of regulation relying on complex and innate conditions of vasoregulation in control children[45] and in children with a diagnosis of ADHD.[46] Challenges concerning functional aspects of the brain are often due to developmental factors, the occurrence of different levels of impairment, large inter-individual differences, and lack of controlled normative data. This study is no exception; the lack of control norms to establish a hypothetical ideal rest-state phase synchronization status for children in this age range will be subject of future research.

Our investigation and interpretation of spontaneous oscillations of cerebral perfusion is different from those of previous studies. The reason for this is that we looked at phase synchronization in children with ADHD analyzing the phase vectors in terms of spatial shifts between adjacent but different cortical regions during a modified laboratory school protocol that controls the specific timing of the medication peak of efficacy. The timing of NIRS measurements for sessions 2 and 3 occurred at medication peak-time following known onset effects of treatment to ensure maximal pharmacological efficacy.[25,26]

Endogenous mechanisms of brain regulation and integration of HbO_2 and HHb activity involve simultaneous and time variant responses and spatially reciprocal responses. Reciprocity refers to the oscillatory behavior of spontaneous hemoglobin fluctuations occurring between two different areas of the frontal cortex.[47,48] This approach aims to establish how the phase of the hemodynamic waves shows differences between the frontal lobes that can be used to identify cortico-vascular networks of activation. The imaging literature has identified a default network of rest state in those with attention problems,[5,49,50] and we also know that fluctuations at rest are significantly larger than during activation due to mental effort.[51] Thus, we found that cerebral oxygenation would be locally organized and that the oxygen metabolism would respond to stimulant medication by reorganizing local blood supply. The present interpretation of the results takes into account the interplay between local and global regulation of oxygen delivery. Although we had no specific hypothesis about the phase synchronization of HbO_2 and HHb, these results are in support of a reciprocal rearrangement of neurovascular activation. We did not study phase change between oscillations. Low frequency waves of cerebral perfusion have been linked to effects of intracranial[52] arterial blood pressure and sympathetic neural oscillations.[53] Their purpose is to regulate spontaneous hemoglobin oscillations at a systemic level, but they have also recently become relevant for explaining how the brain organizes its neurons into cooperating groups.[47]

Our results support the idea that hemoglobin phase locking between different volumes of the frontal brain area is the result of information processing; in our case the phase modulation changed based on "information" carried by the physiological response to stimulant medication that induced a phase shift.

Our findings constitute another step toward establishing a rationale for mental activation in children with a diagnosis of ADHD. Other studies have successfully investigated the concept of "information moving between brain areas" using other methods[40,45,46] and found that brain networks are efficient in activating larger number of brain areas as task complexity also increases in a hierarchical manner. It has been found that this modality works by phase synchronization of different areas, hence allowing coordination of information travelling through the brain.[9]

In our study phase synchronization reveals a property of cortical communication between close but independent brain regions; if stimulant medication improves dopamine reuptake

in the brain, then hemoglobin oscillations are reorganized toward a phase synchronization somehow different from the initial about 0-deg. and approximately −90- deg. (about 240-deg.) for the oxy and deoxy hemoglobin, respectively. This constitutes further evidence that "information" carried by phase synchronization in the brain is a sensitive measure of local metabolism and perfusion due to activation at rest. Our results should be compared with other findings to elaborate a prediction, but little is available in the literature. It is worth noting that the work of Laird and colleagues have compared the interrelation between phases in an fMRI study, using finger tapping, and successfully established a relationship between the reference function and the instantaneous phases.[48] Hence the study of the phase synchronization is a promising method to investigate relationships between signals, not of signals themselves, which has shown that relationships between phases occur even if the signals have no interdependence. Our results may provide preliminary guidelines for the interpretation of brain hemodynamics using NIRS in children with ADHD. The phase synchronization of time series oscillating in different cortical regions can detect reciprocal interactions due to medication-induced changes between the left and right regions of the frontal brain, a region of the dopaminergic pathway of the default-mode network.

5 Conclusion

Phase synchronization revealed region specific reorganization of oxy- and deoxy-hemoglobin oscillations following stimulant medication treatment of behavioral symptoms of ADHD, thus allowing controlling medication efficacy noninvasively and in real-time. The neurovascular pattern of information integration in the frontal cortex during baseline, with no defined cognitive task, is differentiated by medication status. The underlying process responsible for the selective preference of phase synchronicity needs further investigation. Medication may result in a different way of controlling the spontaneous fluctuations in the frontal cortex. Alternatively or additionally, medication may improve the recruitment of regional tissue neurovasculature. Although these findings could be specific to ADHD, they offer a window to our understanding of the functional use of near-infrared spectroscopy for the characterization of physiological alterations in brain tissue due to mental health condition and/or psychopharmacology. In principle, such non-invasive measurements can be repeated multiple times across a day in addition to "at baseline" to see if changes in phase synchronization relate to time course effects. Future studies should continue to build on the known fundamental cyclical variations of neurochemical processes of the brain, localized within an established network of regions during the baseline or 'default mode' state of brain function.

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