A WAVELET ANALYSIS OF BOLD SIGNALS OBTAINED IN MR STUDIES FOR ADHD DIAGNOSIS

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Abstract

A series of wavelet analysis techniques were applied to the Blood Oxygen Level Dependent (BOLD) signals of Functional Magnetic Resonance Images (fMRI) of healthy children and a group diagnosed with Attention deficit hyperactivity disorder (ADHD). Imaging was performed on a total of 15 subjects (ages between 4 – 13 years) divided into Healthy (H) and ADHD (AD) groups. The 1.5T Philips scanner from ``Hospital Infantil de México Federico Gómez´´ was used to obtain data. Statistically significant differences were found for the wavelet scale and the frequency parameters between the H and the AD groups. These results point towards the future use of these techniques as diagnostic tools.

Keywords: Wavelets, BOLD, ADHD, Diagnosis

Introduction

ADHD is one of the most common mental disorders in childhood, affecting 5 - 10% of children all over the world (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). ADHD is characterized by inappropriate levels of inattention, impulsivity, and hyperactivity. It frequently persists well into

adolescence or even adulthood (Biederman, 1998) with a prevalence at those ages of approximately 4% (Biederman, 2005). Currently the diagnosis of this disease is done through vague, open to interpretation psychological examinations and questionnaires (DSM-5 Conner´s and ADHD-RS). Nowadays there are no definitive studies (including imaging studies), which can help diagnose this disorder (Y.T. Kitamura, 2008). ADHD has three subtypes: predominantly inattentive, predominantly hyperactive-impulsive, and combined (Fernández Parra, 2005). It is thought that 80% of the origin of this disorder is genetic and just 20% social (Polanczyk et al., 2007). At a neurological level it has been known to affect the dopaminergic and noradrenergic systems and structures of the brain and medication has been designed to address these regions (Engert & Pruessner, 2008).

The development of methods to study human brain structure and function in vivo has been one of the greatest landmarks of medical research in the last century. Nowadays there is a large number of techniques for this purpose, each with their own advantages and disadvantages. This different functionality enables different types of research questions to be investigated (Paloyelis, Mehta, Kuntsi, & Asherson, 2007). Some of these functional neuroimaging techniques have been used to study the pathophysiology that underlies ADHD. The ones most commonly used are: Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) and BOLD functional MRI (fMRI). Application of these technologies has focused on resting state studies. During these studies the patient lies awake but inactive inside the scanner while brain function is measured. SPECT and PET studies have reported abnormalities in the frontal cortex (Lee et al., 2005), striatum (Lou, Henriksen, & Bruhn, 1990), anterior cingulate cortex (Langleben et al., 2002), sensorimotor cortex (Lee et al., 2005), occipital cortex (Schweitzer et al., 2003) and cerebellum (Lee et al., 2005).

The most common contrast source in fMRI studies is BOLD signal. BOLD signal fMRI provides an indirect measurement of neural activity as it detects the hemodynamic response of brain´s blood supply to active neurons. BOLD was first used for imaging by Ogawa et al. in 1992 (Ogawa et al., 1992) and its signal is generated by changes in the ratio of oxygenated to deoxygenated haemoglobin (oHb and dHb respectively). Increases in neural activity in a given region change the balance of oHb and dHb. MR scanners are able to detect these differences; therefore they can pinpoint regions of activity in the brain during a certain activity. As in the case of Nuclear Medicine, MR and fMRI have been used in the past to study ADHD, some results are highlighted in the following reviews (Castellanos & Proal, 2012) (Tian et al., 2006). A recent publication by de Celis Alonso et al. (de Celis Alonso et al., 2014) showed that MR resting states affects many

dopaminergic regions, the cerebellum, mid-frontal lobes, executive function regions, precuneus, cuneus and the clacarine fissure. Nevertheless and even considering all the work described above, the distinction between H and AD patients or even more, the distinction between the three subgroups of ADHD has still not been possible using these technologies.

Wavelet analysis methods are the result of collective efforts in the field of mathematics that were independently developed and investigated by distinct research groups (Unser, 1996). The first reference to the wavelet transform is the Haar wavelet proposed by the mathematician Alfred Haar in 1909 (S. Mallat, 2008). Almost 75 years later physicist Alex Grossman established the term wavelet in 1984. In 1985, the Haar wavelet was the only orthogonal wavelet known; Nevertheless, the mathematician Yves Meyer constructed the second orthogonal wavelet called Meyer wavelet in 1985 (S. G. Mallat, 1989). Nowadays there are hundreds of different wavelets.

Wavelet methods provide a unifying framework to decompose images, volumes and time-series data into their elementary constituents across scales. They have a large body of applications which include: Data de-noising, reduction of space for data storing, numerical analysis solutions, edge detection and graphic creation (P.S. Addison, 2002). Although a relatively recent construct, wavelets have become a tool of choice for engineers, physicists, and mathematicians. One of the consequences of this is that wavelet methods of analysis and representations are presently having a significant impact on the science of medical imaging and the diagnosis of disease. Some of these applications used in the MRI field are the novel acquisition methods using wavelet encoded MRI (Y.T. Kitamura, 2008). The continuous wavelet transform (CWT) is a popular analysis tool (S. G. Mallat, 1989) (S. Mallat, 2008). It has been applied in the past to fMRI analysis as a de-noising step during image pre-processing (Hilton, 1996) (Wink & Roerdink, 2004). Temporal correlation between fMRI data has also been proposed using wavelets (Bullmore et al., 2001) (Bullmore et al., 2003) (Fadili & Bullmore, 2002) (Woolrich, Ripley, Brady, & Smith, 2001). Finally, La Conte at al. (LaConte, Ngan, & Hu, 2000) have developed and demonstrated a de-noising methodology for event related fMRI data using a method based on the Wiener filtering in the wavelet domain. It has been shown that wavelet analysis improved connectivity analysis (Guo et al., 2012) and it has been applied to Alzheimers (Supekar, Menon, Rubin, Musen, & Greicius, 2008) as well as stress studies (Yashima, Sasaki, Kageyama, Odagaki, & Hosaka, 2005). To our knowledge, no specific publications in which wavelet analysis was directly applied to resting state analysis of ADHD patients was found.

From all the wavelet methodologies the CWT is of most interest for this study as it allows the analysis of a signal as a whole or as a fraction. In

general the CWT can be understood as a continuous signal convolved with a mother wavelet function Ψ(t) (Farge, 1992). By definition a mother wavelet must belong to the space $L^2(R)$ of localized functions (must be finite), and the integral of the square function must have a real value (*E*).

$$f \in L^2 \rightarrow \int \int |f(t)^2| dt = E < \infty \quad (1)$$

When convolving the mother wavelet with the signal we obtain the CWT coefficients or scales. Therefore a coefficient can be described as the convolution of the mother wavelet by the signal for a given time point. Then the mother wavelet moves to the next time point and repeats the process. Once all the time points are covered the convolution process begins again at time 0 with a mother wavelet that has been modified from the original by dilating or contracting it. The shape modification of the mother wavelet is controlled by a parameter named *a*. What has just been explained is what happens when a 1D signal is being used (i.e. the variation of the signal with time), if the data were 2D for example, an image, the wavelet calculation would be executed in two dimensions according to the expression 2.

$$\Psi_{(a,b)}(t) = \frac{1}{\sqrt{a}} \Psi \left(\frac{t-b}{a} \right) \quad (2)$$

In which $\Psi_{(a,b)}(t)$ is the mother wavelet, ***a*** is the contraction/expansion parameter as defined before and ***b*** is a new parameter which corresponds to displacement in the second dimension. Ψ is a base function that will change depending on the wavelet used.

Therefore, the continuous wavelet transform of a signal *f(t)*, with a scale ***a*** and at position ***b***, is calculated by the convolution of *f(t)* with $\Psi_{(a,b)}(t)$ according to the following expression:

$$CWT\big(F(t(a,b))\big) = \int_{-\infty}^{+\infty} f(t) \frac{1}{\sqrt{a}} \Psi \left(\frac{t-b}{a} \right) dt \quad (3)$$

In which *f(t)* is the original signal and (a, b) are the wavelet scales. When working in 1D, Eq. 3 is modified by considering the ***b*** parameter as a constant and the CWT scales will be dependent only on *t* and ***a***.

Other wavelet techniques that can be used for image and signal analysis are related to frequency calculations. In these we calculate characteristic wavelet frequencies with equation:

$$CWT(F\big(t(a,b)\big) = \int_{-\infty}^{+\infty} \hat{f}(t) \sqrt{a} \Psi^*(a,\omega) e^{i\omega b} d\omega \quad (4)$$

In this equation Ψ^* is the complex conjugate of the mother wavelet function as defined in Eq. 2, ***a*** and ***b*** are parameters as defined before, $\hat{f}(t)$is the complex conjugate of the signal and $CWT(F\big(t(a,b)\big)$ are the frequencies in wavelet space (normal space) which are equivalent to scales but were calculated in Fourier space. Frequencies are inversely proportional to scales as:

$$\omega = \frac{c}{a} \quad (5)$$

In which ***a*** is the parameter defined before and ***c*** is a constant.

As it is the case for all other imaging techniques, low frequencies obtained with these calculations correspond to low resolution details in the original data. In contrast, high frequencies correspond to high image details.

The main objective behind this work was to use the capabilities of wavelet analysis (scales and frequencies) to study BOLD information obtained from children with and without ADHD. The idea was to find biomarkers in the brain during resting state studies with fMRI which could be used to diagnose the disorder in children. A finding of this type should improve medical attention, reduce its costs and improve life quality of patients with this disorder.

Methods

Volunteers: All experiments were performed according to international conventions for biomedical studies on humans. Experimental measurements were obtained in the ``Hospital Infantil de México Federico Gómez´´. All volunteers were children ranging from 4 to 13 years old; with an average age of 8.6 ± 2.1 years (mean ± standard deviation). All patients were male, right handed and selected randomly from the population of the hospital. Eight AD patients together with nine H volunteers were used for this study. All ADHD volunteers had never been medicated before for this disorder and were diagnosed by medical doctors in-house. Only volunteers with ADHD of the inattentive and the impulsivity-hyperactivity subtypes were considered for the study. Control volunteers were completely healthy at the time of the study, with no history of any previous psychological or mental disorder and no prior neurological interventions. No intelligence matching between groups was performed.

Equipment: Experiments were performed on a 1.5 T Philips Intera-Achieva scanner (Philips, Inc., Netherlands), using an 8 channel SENSE head-coil. Gradient coils were NOVA (Copley 271 Dual, slew rate 80 mT/m/ms, peak amplitude 120 mT/m).

Protocol: Resting state scans were acquired immediately after standard setup of the scanner. The patient lied during the study in a supine position inside the scanner with closed eyes (but always awake). The resting state sequence was the first one to be run on all patients for a period of 7 minutes 25 seconds. Following this sequence a fast anatomical image was acquired during a period of 3 minutes 10 seconds. Once these sequences were acquired, patients were extracted from the scanner.

MRI sequences: Resting State: 150 whole brain volumes, comprising 35 coronal slices covering the whole of the brain (including the cerebellum) were acquired with a fast-echo EPI sequence. TR=2.9 s, TE=50 ms, 90° flip angle, 64 x 64 matrix with a 3.6 x 3.6 mm in-plane resolution and 4 mm slice

thickness (no gap between slices). Anatomical images were acquired with a 3D T_1-weighted gradient echo sequence (TR=307.81 ms, TE=2.48 ms, 4 repetitions and 80° flip angle). Sequences covered the same FOV with a 640 x 640 matrix which gave a 0.36 x 0.36 mm in-plane resolution (interpolated) and 4 mm slice thickness (also no gap between slices).

Data analysis: Resting state data analysis was performed with: Data Processing Assistant for Resting State fMRI Advanced edition (DPARSFA-V2.2; http: //www.restf mri.net), Resting-State fMRI Data Analysis Toolkit (REST1.8; http://www.restf mri.net) All these software programs were run on a Statistical Parametric Mapping platform (SPM8; http : www.fil.ion.ucl.ac.uk/spm), based on the Matlab programming language (The Mathworks Inc., USA).

For each one volunteer, the 150 images from the resting state sequence were converted to DICOM format to work with them in SPM8 and DPARSFA. The first 5 images were eliminated from the analysis to enable the longitudinal magnetization to reach a steady state and remain stable during the analysis. Images were then slice time corrected, realigned, normalized to an EPI.nii template built in the Montreal Neurological Institute (MNI) coordinates, and finally smoothed with a (7,7,8) mm Kernel. On the other hand anatomical images were segmented into white and grey matter, skull and CSF liquid. This information was normalized with the same template as before and was used to mask resting state data eliminating all but the grey matter information from data. Finally an Automated Anatomic Labelling mask (AAL atlas) was used to segment the resting state data into 116 different brain regions. All the voxels that belonged to a given region (i.e. cerebellum 8) were then averaged and a time trend of BOLD signal with 145 time points (one per volume scanned) was obtained. This time data from each region was then analysed using wavelets corresponding to *f(t)* in equations (1) to (5).

Wavelet Analysis: A CWT analysis was applied to the BOLD signals from the cerebellum and the lenticular nucleus. These two regions were selected as they are known to be affected by ADHD in children is (de Celis Alonso et al., 2014). In this study the Mexican Hat was used as a base function defined as follows:

$$\Psi(t) = C(1 - t^2)e^{\frac{-t^2}{2}} \quad (6)$$

where $C=(2/\sqrt{3})\pi^{-1/4(-1)}$ is a constant. This function is proportional to the second derivative function of a Gaussian probability density function. It was selected because it looks like the signal analysed, it is continuous(G. Erlebacher, 1996). This is the function that will be used for scale and frequency calculations using Equations (3) and (4) respectively. All

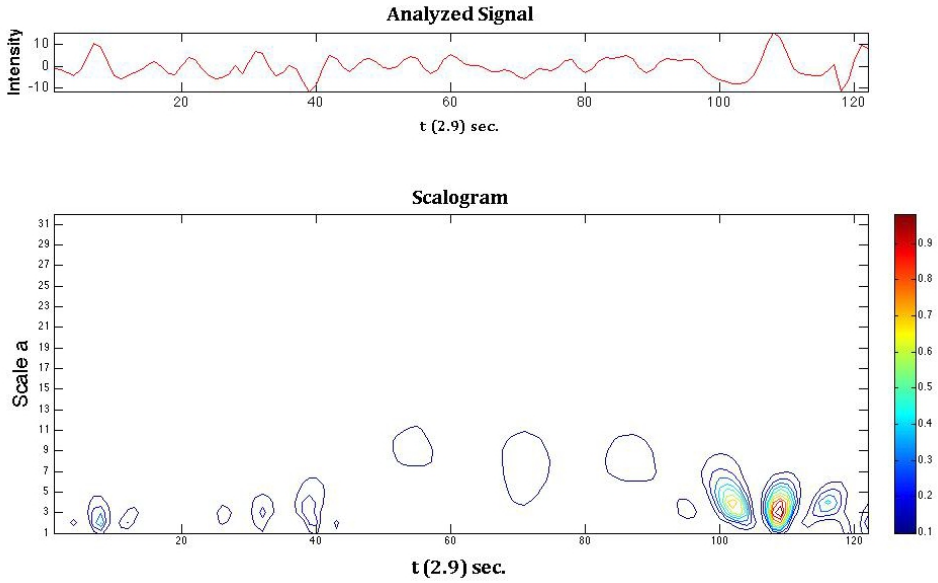
calculations were performed using a Matlab® platform custom and routines specifically written for this purpose.

Statistics. All data obtained from volunteers in this study proved to be parametric after statistical testing (normality and equal variance tests). Therefore, when comparing two groups T–tests were used to find differences between them. A standard $p<0.05$ was used as threshold of significance.

Results

A 1D wavelet transform on the BOLD fMRI time evolution of the 8th region of cerebellum (regions 103 and 104 from AAL atlas) and the lenticular nucleus (regions 75 and 76 of the AAL atlas) of children diagnosed with ADHD and H control children was performed. These two regions (four when left and right hemisphere structures are considered) are known to be affected by ADHD (Engert & Pruessner, 2008).

Wavelet scale calculations (Eq. 3) can be represented as scalograms. In these graphs time vs. wavelet scale are plotted, (Figure 1, scalogram of the cerebellum 8 region). These images correspond to two children one with ADHD and the other a control, both 8 years old. The time series for the studied structures in children with ADHD were characterized by big wavelet scales while the structures corresponding to healthy children were characterized by small scales. This is a trend which is observed for all patients in this study (data not shown here). In order to quantify this finding single subject analysis was performed.



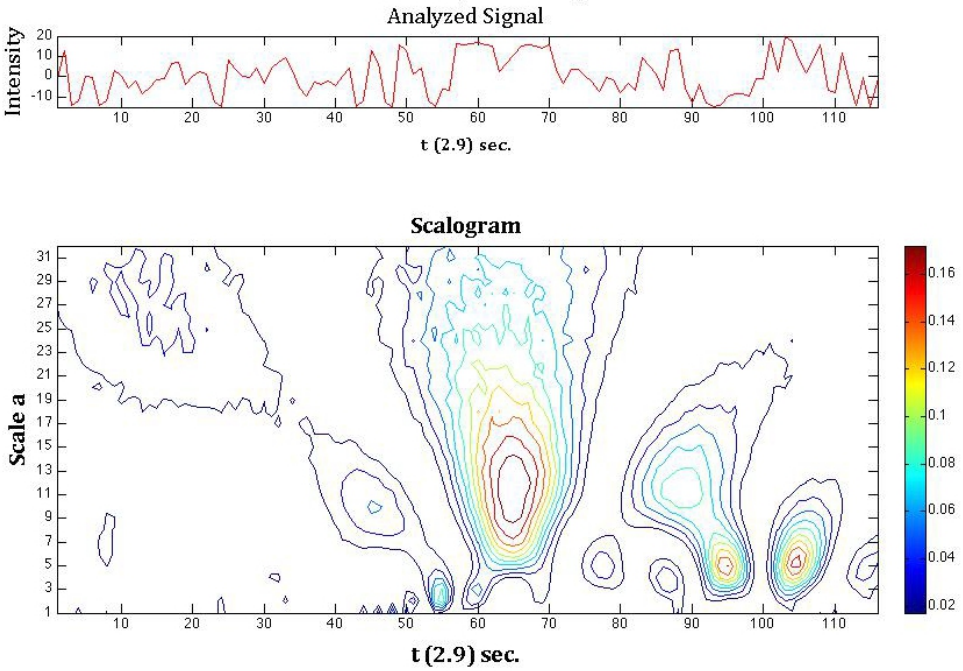


Figure 1. Scalogram and scales from CWT transformation of BOLD data.

In this figure the results of a 1D wavelet transform of BOLD time sequences can be observed. Information is divided into four panels. The small ones represent the time evolution of the BOLD signal for a given region over experimental time (*f(t)*). The large panels are scalograms in which wavelet scales are confronted with the time. The wavelet analysis in this case corresponds to a healthy child (top two images) and a child with ADHD (bottom two images). Both volunteers were matched in age (8 years old). Pseudo-colouring in sonograms has no scientific implications and it just represents concentration of scale values.

Figure 2 presents the total wavelet scale *a* in arbitrary units obtained from Eq. 3 vs. age (years). Results are presented for both structures, cerebellum (Fig. 2A) and lenticular nucleus (Fig 2B). In this image data for the H and the AD groups are presented together and categorized by ages (AD with empty circles and H with black full circles). It can be appreciated that the results for the youngest and oldest children are very similar. In contrast clear differences between Healthy and ADHD children in the age range from 7 to 10 years were found. In this situation the ADHD children showed more activity (higher wavelet scale) than their H counterparts. In all cases AD patients presented larger values for their wavelet scale when compared to H controls (at a given age). The significance of this difference was calculated and found to exist with a $p<0.02$ (T-tests, result valid for both cerebellum and lenticular regions).

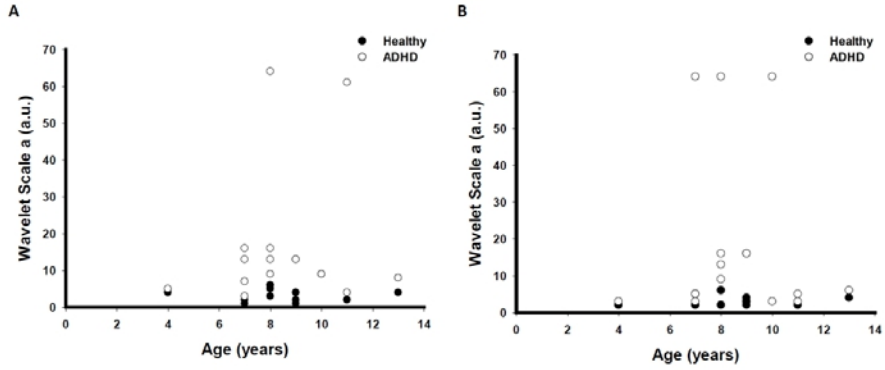


Figure 2. Wavelet scale vs. age.

In these two graphs wavelet scales values vs. age of H and AD children are presented. AD children data are shown with empty circles and H children data with black full circles. Results are obtained for the 8th region of cerebellum (2A) and from the lenticular nucleus (2B). There is double amount of data (n=16 for AD and n=18 for H) as left and right hemisphere results are displayed.

Figure 3 presents the characteristic frequencies (a-dimensional) of each volunteer obtained with Eq. 4 vs. the wavelet scale obtained from Eq. 3. Here data for the H and the AD groups are presented together (AD with empty circles and H with black full circles). It can be seen that ADHD patients presented, in general, shorter frequency values than H controls (calculation independent of age). The significance of this difference was calculated and found to exist with a $p<0.005$ (T-test, valid for both cerebellum and lenticular regions).

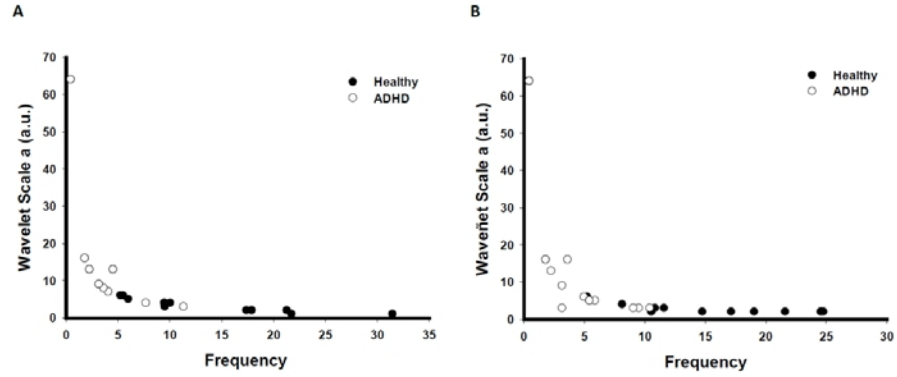


Figure 3. Wavelet scale vs. wavelet frequency.

The results for the 8th region of the cerebellum (left and right hemispheres as before) are presented in the left panel (3A). AD children data are shown with empty circles and H children data with black full circles. Results for the lenticular nucleus (left and right hemispheres as before) are presented in the right panel (3B) in the same manner as before.

Discussion and Conclusion

In this work we have been able to differentiate H children from AD using fMRI - BOLD signal and wavelet analysis. Differences were statistically significant and could be found between groups when considering the scale parameter used in wavelet analysis (Figure 2). Here all ADHD children had higher values compared to their age matched H counterparts. When comparing the scales and frequencies of wavelet analysis for both groups (Figure 3) we also found that the AD group presented significantly shorter frequencies.

Nevertheless limitations to this study should be considered. The main limitation for this work was the reduced size of the sample. Even if the calculated beta power value of this study reached 0.8 which makes it acceptable, a greater sample should be used in the future to confirm these results. Additionally in order to discriminate between the three subtypes of ADHD we would need a larger data sample. The main problem with this kind of studies and with this type of disorders rises because of the large amount of variables that can affect the outcome of a diagnostic image. In this case sex and age have already been proved to affect imaging results. But not just those: IQ, dexterity, secondary deficiencies associated with the disorder (i.e. mental retardation), social environment and the eternally discussed genetic factor can all alter the resulting image. This creates the necessity of using large databases to clearly establish the physiological basis of the disorder. An example of efforts in this area is the ADHD 200 global competition (http://fcon_1000.projects.nitrc.org/indi/adhd200/) which has been able to identify the illness with a maximum efficiency till now of 69.59% (Dey, Rao, & Shah, 2012).

Another arguable factor in this study is the use of one single mother wavelet function (Mexican Hat). We actually used the Daubechies wavelet as a first approximation to this analysis but no relevant differences between groups were found. In addition, when performing wavelet analysis it is important that the mother function be similar to the signal being analysed (G. Erlebacher, 1996). The Mexican Hat was selected as it is continuous as the BOLD signal, has no cuts on it and the topology is similar. As a matter of fact the results found here suggest a wavelet specific for the goals of this work could be found. A wavelet designed to highlight, for example, differences in the anatomy of certain landmarks or in the measured activity of a region (measurements not made with BOLD but with nuclear medicine technologies like PET and SPECT). Then this analysis could be performed in a different way and results could be used to build a model that gives diagnostics with a 100% accuracy (actual accuracy is close to 69.59% in previous studies) (Dey et al., 2012).

From the results shown in Figure 2 it is evident that children in the extremes of the age range of our study presented small differences between the healthy and ADHD groups. First, this could be an effect of the low size of this sub sample that exists (n=8 children in total). Disregarding this fact, one can make some logic out of this considering that young patients in their toddler years have not yet developed the behaviour and habits that would characterize them as ADHD. Therefore the difference in brain physiology must be small when compared to healthy children. On the other side of the spectrum, children close to their teens, through social interaction with friends and family have probably learnt to condition and control their behaviour. This socially induced control results in changes in brain function. This has two rather relevant implications. Firstly the results of the analysis presented here show brain plasticity. This makes the methodology even more relevant as brain plasticity is very difficult to measure with imaging technologies. Secondly, the effect of the 20% social component associated with this disorder, if modulated properly, could help eliminate the problems associated with the latter. This means that the psychological aspects of the disorder are completely relevant and is in this area that research should be focused for future treatments.

Larger wavelet scale factors were observed for ADHD patients when compared to Healthy volunteers (Figures 1 and 2). These scales present the point in which the convolution between BOLD signal and the mother wavelet is larger. This indicated that BOLD signals convolved better with a shorter and more abrupt MH functions than with a flat and long lasting mother wavelet. Even if highly speculative, this could point towards a more "chaotic" or disordered neuronal behaviour which affected the BOLD signal considerably, producing sharp changes in it. Nevertheless, future work with wavelets specifically developed for BOLD analysis as well as larger samples of volunteers would help elucidate the results and hypothesis presented in this work.

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References:

Biederman, J. (1998). Attention-deficit/hyperactivity disorder: a life-span perspective. [Research Support, Non-U.S. Gov't

Review]. *J Clin Psychiatry, 59 Suppl 7*, 4-16.
Biederman, J. (2005). Attention-deficit/hyperactivity disorder: a selective overview. [Review]. *Biol Psychiatry, 57*(11), 1215-1220. doi: 10.1016/j.biopsych.2004.10.020
Bullmore, E., Fadili, J., Breakspear, M., Salvador, R., Suckling, J., & Brammer, M. (2003). Wavelets and statistical analysis of functional magnetic resonance images of the human brain. [Research Support, Non-U.S. Gov't
Review]. *Stat Methods Med Res, 12*(5), 375-399.
Bullmore, E., Long, C., Suckling, J., Fadili, J., Calvert, G., Zelaya, F., . . . Brammer, M. (2001). Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. [Research Support, Non-U.S. Gov't]. *Hum Brain Mapp, 12*(2), 61-78.
Castellanos, F. X., & Proal, E. (2012). Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. [Review]. *Trends Cogn Sci, 16*(1), 17-26. doi: 10.1016/j.tics.2011.11.007
de Celis Alonso, B., Hidalgo Tobon, S., Dies Suarez, P., Garcia Flores, J., de Celis Carrillo, B., & Barragan Perez, E. (2014). A Multi-Methodological MR Resting State Network Analysis to Assess the Changes in Brain Physiology of Children with ADHD. *PLoS One, 9*(6), e99119. doi: 10.1371/journal.pone.0099119
Dey, S., Rao, A. R., & Shah, M. (2012). Exploiting the brain's network structure in identifying ADHD subjects. *Front Syst Neurosci, 6*, 75. doi: 10.3389/fnsys.2012.00075
Engert, V., & Pruessner, J. C. (2008). Dopaminergic and noradrenergic contributions to functionality in ADHD: the role of methylphenidate. *Curr Neuropharmacol, 6*(4), 322-328. doi: 10.2174/157015908787386069
Fadili, M. J., & Bullmore, E. T. (2002). Wavelet-generalized least squares: a new BLU estimator of linear regression models with 1/f errors. *Neuroimage, 15*(1), 217-232. doi: 10.1006/nimg.2001.0955
Farge, M. (1992). Wavelet transforms and their applications to turbulence. *Annu. Rev. Fluid Mech.,, 24*.
Fernández Parra, A. (2005). *Manual de recursos para la evaluación y tratamiento de niños con problemas de conducta*: Ed Distribuciones Reprográficas Granada.
G. Erlebacher, M. Y. H., L.M. Jameson. (1996). *Wavelets, Theory and Applications*. Oxford, Reino Unido: Oxford University Press
Guo, C. C., Kurth, F., Zhou, J., Mayer, E. A., Eickhoff, S. B., Kramer, J. H., & Seeley, W. W. (2012). One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. [Research Support, Non-U.S.

Gov't]. *Neuroimage, 61*(4), 1471-1483. doi: 10.1016/j.neuroimage.2012.03.027
Hilton, M., Ogden, T., Hattery, D., Eden, G., Jawerth, B. (1996). *Wavelets in Medicine and Biology* CRC Press.
LaConte, S. M., Ngan, S. C., & Hu, X. (2000). Wavelet transform-based Wiener filtering of event-related fMRI data. [Research Support, U.S. Gov't, P.H.S.]. *Magn Reson Med, 44*(5), 746-757.
Langleben, D. D., Acton, P. D., Austin, G., Elman, I., Krikorian, G., Monterosso, J. R., . . . Strauss, H. W. (2002). Effects of methylphenidate discontinuation on cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. [Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.]. *J Nucl Med, 43*(12), 1624-1629.
Lee, J. S., Kim, B. N., Kang, E., Lee, D. S., Kim, Y. K., Chung, J. K., . . . Cho, S. C. (2005). Regional cerebral blood flow in children with attention deficit hyperactivity disorder: comparison before and after methylphenidate treatment. [Comparative Study
Research Support, Non-U.S. Gov't]. *Hum Brain Mapp, 24*(3), 157-164. doi: 10.1002/hbm.20067
Lou, H. C., Henriksen, L., & Bruhn, P. (1990). Focal cerebral dysfunction in developmental learning disabilities. [Comparative Study]. *Lancet, 335*(8680), 8-11.
Mallat, S. (2008). *Wavelet Tour of Signal Processing*. Burñington, MA, USA: Elsevier.
Mallat, S. G. (1989). Multifrequency channel decompositions of images and wavelet models *IEEE Transactions on Acoustics, Speech and Signal Processing., 37*(10), 2091 - 2110.
Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. [Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.]. *Proc Natl Acad Sci U S A, 89*(13), 5951-5955.
P.S. Addison, J. N. W., T. Feng. (2002). LOW-OSCILLATION COMPLEX WAVELETS. [Regular Article]. *Journal of Sound and Vibration, 254*(4), 733-762.
Paloyelis, Y., Mehta, M. A., Kuntsi, J., & Asherson, P. (2007). Functional MRI in ADHD: a systematic literature review. [Review]. *Expert Rev Neurother, 7*(10), 1337-1356. doi: 10.1586/14737175.7.10.1337
Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. [Meta-Analysis
Research Support, Non-U.S. Gov't

Review]. *Am J Psychiatry, 164*(6), 942-948. doi: 10.1176/appi.ajp.164.6.942
Schweitzer, J. B., Lee, D. O., Hanford, R. B., Tagamets, M. A., Hoffman, J. M., Grafton, S. T., & Kilts, C. D. (2003). A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. [Comparative Study
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.]. *Neuropsychopharmacology, 28*(5), 967-973. doi: 10.1038/sj.npp.1300110
Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. *PLoS Comput Biol, 4*(6), e1000100. doi: 10.1371/journal.pcbi.1000100
Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., . . . Zhuo, Y. (2006). Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. [Comparative Study
Research Support, Non-U.S. Gov't]. *Neurosci Lett, 400*(1-2), 39-43. doi: 10.1016/j.neulet.2006.02.022
Unser, M. (1996). *A Practical Guide to the Implementation of the Wavelet Transform* Boca Raton. FL, USA: CRC Press.
Wink, A. M., & Roerdink, J. B. (2004). Denoising functional MR images: a comparison of wavelet denoising and Gaussian smoothing. [Comparative Study
Evaluation Studies
Research Support, Non-U.S. Gov't
Validation Studies]. *IEEE Trans Med Imaging, 23*(3), 374-387. doi: 10.1109/TMI.2004.824234
Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. [Research Support, Non-U.S. Gov't]. *Neuroimage, 14*(6), 1370-1386. doi: 10.1006/nimg.2001.0931
Y.T. Kitamura, T. Y. Y. H. (2008). Hemodynamic Response Latency Analysis Using Wavelet Transform in Event-related Functional MRI. *International Journal of Intelligent Computing in Medical Sciences & Image Processing, 2*(3).
Yashima, K., Sasaki, T., Kageyama, Y., Odagaki, M., & Hosaka, H. (2005). Application of wavelet analysis to the plethysmogram for the evaluation of mental stress. *Conf Proc IEEE Eng Med Biol Soc, 3*, 2781-2784. doi: 10.1109/IEMBS.2005.1617049