ABSTRACT

- Purpose: Hemodialysis (HD) is considered the most common alternative for overcoming renal failure. Studies have shown the involvement of HD membrane in the genesis of oxidative stress (OS) which has a direct impact on the brain tissue and is expected to be involved in brain plasticity and also reorganization of brain function control. The goal of this paper was to demonstrate the sensitivity of the blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) to characterize the OS before and after the HD session. Patients, materials and methods: Twelve male patient-volunteers following chronic HD for more than 6 months were recruited among 86 HD-patients. All patients underwent identical assessment immediately before and after the full HD-session. This consisted of full biological assessment, including malondialdehyde (MDA) and total antioxidant activity (TAOA); and brain BOLD-fMRI using the motor paradigm in block-design. Results: Functional BOLD-fMRI maps of motor area M1 were obtained from the HD patient before and after the hemodialysis session, important decrease in the intensity of brain activation of the motor area after HD, and important increase of the size of the volume of brain activation were observed, these changes are reflecting brain plasticity that is well correlated to OS levels. Individual patients MDA and TAOA before and after the hemodialysis sessions demonstrated a clear and systematic increase of the OS after HD (P-value = 0.03). Correlation of BOLD-fMRI maximal signal intensity and volume of activated cortical brain area behaviors to MDA and total TAOA were close to 1. Conclusion: OS is systematically increased in HD-patients after the HD-process. Indeed, the BOLD-fMRI shows a remarkable sensitivity to brain plasticity studied cortical areas. Our results confirm the superiority of the BOLD-fMRI quantities compared to the biological method used for assessing the OS while not being specific, and reflect the increase in OS generated by the HD. BOLD-fMRI is expected to be a suitable tool for evaluating the plasticity process evolution in hemodialysis brain patients. © 2014 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: hemodialysis, oxidative stress, BOLD-fMRI, brain function, functional control, plasticity.

INTRODUCTION

Hemodialysis (HD) is considered the most common alternative for overcoming renal failure (Himmelfarb and Ikizler, 2010; Farzaneh et al., 2012). However, this blood-processing procedure contributes significantly to producing oxidants and elevated markers of lipid peroxidations (Siddique et al., 2012). Malondialdehyde (MDA) is one of the major reactive substances resulting from this peroxidation (Amedeo et al., 2009) quantified by the thiobarbituric acid reactive substance (TBARS) assay, a method used for assessing the oxidative stress (OS) while not being specific (Del Rio et al., 2005; Siddique et al., 2012).

Indeed, oxygen supplied by the blood oxygenation process is behind the OS phenomena whenever the control systems of metabolites generated are suffering or corrupted (Kohen and Nyska, 2002). Thus, multiple cellular defects are observed and might result in the release of pro-inflammatory and inflammatory factors, factors that promote cell proliferation, and apoptosis and/or necrosis (Lara et al., 2004; Libetta et al., 2011). The enhancement of the cell infarct might yield later various diseases such as cardiovascular disease, cancer, inflammatory and neurodegenerative diseases (Simone et al., 2010). Besides, the brain has a very high oxidative...
metabolism, which is involved in producing a large amount of reactive oxygen substances (ROS). Recent papers suggested that HD has the potential of possible additional risk factor for cognitive decline (McQuillan and Jassal, 2010; Rizzo et al., 2012).

Consequently, the OS has a direct impact on the brain tissue since it is involved in most metabolic processes discussed so far (Noseworthy and Bray, 1998; Hanafy and Selim, 2012). Hence, the OS is expected to be involved in brain plasticity and also in brain function control (Kishida and Klann, 2007; Numakawa et al., 2011). Brain plasticity also known as neuroplasticity, represents the amazing ability of the central nervous system to constantly change its structure and function and make a subtle remodeling of the nervous system, it manifests as a heterogeneous spectrum of functional cortical reorganization patterns and is dependent on multiple factors (Kleim and Jones, 2008). Thus, the oxygen level in cortical brain tissue is directly involved in the brain function control (Raichle and Snyder, 2007). In addition, the blood oxygenation level-dependent (BOLD) measurement using magnetic resonance imaging was reported as a non-invasive approach allowing the assessment of the cortical oxygenation during and ‘off functional’ control of the brain (Sørensen et al., 2009). Indeed, the neuronal metabolism is dependent on oxygen supplies by blood because the energy production from glucose is mainly of the aerobic type (Gjedde, 2007; Kumar et al., 2012). The neuronal activity is originating increased oxygen expenditure, hence an important enhancement of the local blood flow expressed as neurovascular coupling (Girouard and Iadecola, 2006; Kikuchi et al., 2010). The increased blood flow being much more important than the increase of the consumption of oxygen, the neuronal activation is translated by a relative increase of the oxygenated hemoglobin compared to deoxygenated hemoglobin in the activated brain area (Logothetis, 2002; Logothetis and Wandell, 2004). This relative reduction in the concentration of deoxygenated hemoglobin that has a paramagnetic effect, is detected by MRI methods and is reflected as a transitional increase of the T2 signal (Uludag et al., 2006; Chavhan et al., 2009). This measuring approach using the principle of the BOLD contrast is known as blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) (Chen and Ogawa, 2000; Kim and Bandettini, 2012). This BOLD-fMRI methodological development was not only used to assess the brain function activity, but it was also used to assess BOLD phenomena that are directly linked to brain activity or to abundance of free radicals (FRs) and increased OS (Djamali et al., 2007). Hence, the goal of this paper was to demonstrate the sensitivity of the BOLD-fMRI to characterize the OS before and after a HD session in patients suffering from chronic renal failure, while the dialysis process was achieved using the Polysulfone membrane, also to investigate whether fMRI with a motor task is a sensitive method to detect changes in BOLD response occurring before and after HD. The hypothesis tested was the following: HD has an impact on OS as well as on brain function that can be measured with fMRI as a change in BOLD response in the primary motor area. In addition, we demonstrate the impact of HD on the OS as well as in the brain function control reorganization in the cortical area. This would be witness of brain plasticity induced by OS. Finally, we do compare the BOLD-fMRI results with earlier findings of biological assessment methods in the same patients already published in the earlier paper.

**EXPERIMENTAL PROCEDURES**

**Patients**

Twelve male patients-volunteers following chronic HD for more than 6 months were initially recruited among 86 patients following HD in the Hemodialysis Center of the University Hospital of Fez, Morocco. The age of patients ranged from 15 to 45 years old with an average age of 31.5 ± 8 years. Patient’s average duration of HD before recruitment was 48.6 ± 25 months. All patients were on dialysis with three sessions per week by membranes Polysulfone. Anticoagulation used is based on sodium heparin; the dose is the same for each patient throughout the entire study. None of the HD patients received antibiotics or other medications or vitamin supplementation during the study. All subjects gave written informed consent. Patient selection was based on specific criteria of exclusion and inclusion. Diabetic, smokers and patients with episodes of infection or treatment with iron or erythropoietin injection were excluded. All patients showing inflammatory disease and/or neurological and motor disorders even minor were not included. In addition, the healthy neurological profile was a must, and serological profile viral hepatitis C, HIV and B of all patients were negative.

Also were excluded from the study patients with C-reactive protein (CRP) > 6 or those who had a history of hospitalization. During the study, one patient has shown that he is uninterested to participate in the study, while two others underwent infectious episodes that did not allow including in this study. Hence, the full study was achieved by nine patients–volunteers, and only eight HD patients were successfully studied.

The first fMRI study and biological test are performed before the HD session and the second study was performed during the same day after the HD session.

**Biological assessment**

All patients underwent identical biological assessment protocol immediately before starting a HD session and immediately after achieving the full HD session in the Hemodialysis Center of the University Hospital of Fez, Morocco. These consisted of assessing the markers of OS such as MDA and total antioxidant activity (TAAO). Markers of OS were determined by measuring the optical density of MDA at 532 nm and the TAOA at 600 nm by a spectrophotometer JASCO V-530 type, in the Laboratory of Pharmacology (Faculty of medicine and Pharmacy of Fez, Fez, Morocco). The detailed results were reported in Medical Doctor Thesis of one of the authors as well as in conference proceedings (Batta et al., 2010).
BOLD-fMRI acquisition protocol

All patients underwent identical brain BOLD-fMRI protocol before starting a HD session and after achieving the full HD session in Hemodialysis Center of the University Hospital of Fez, Fez, Morocco. The images were acquired in the Department of Radiology and Clinical Imaging of the University Hospital of Fez, Fez, Morocco. The brain BOLD functional and anatomical MR images were acquired using a 1.5-Tesla scanner (Signa, General Electric, Milwaukee, United States). The image acquisition was done using single-shot gradient echo echo-planer imaging (GE-EPI) imaging sequence. This approach was shown to be very sensitive to T2 effect generated during BOLD effect reflecting the functional activity of the cortical brain tissue (Chavhan et al., 2009).

The BOLD-fMRI acquisition parameters were echo time TE = 55 ms, repetition time TR = 3000 ms, slice thickness = 5 mm, field of view FOV = 240 mm, 31 axial slices were acquired covering the entire brain. The acquisition matrix size was 128 × 128. Sixty brain volumes were acquired within 3 min. The BOLD-fMRI paradigm consisted of the motor task where the patients are asked to perform finger taping of the right hand.

Data post-processing and imaging result generation

Image processing and statistical analysis were conducted with Statistical Parameter Mapping (Friston, 1995; Friston et al., 1995a,b) version 8 (2008, Wellcome Department of Cognitive Neurology, London UK; http://www.fil.ion.ucl.ac.uk/spm). All volumes obtained were used for data analysis. The pre-processing with SPM8 included realignment, co-registration: the fMRI images were co-registered to the patient’s own T1 images “each patient had its own anatomical image”, and spatial normalization (template of Montreal Neurological Institute, MNI).

The echo-planar images were realigned using a rigid body transformation to the first volume of the time series for each subject. After this, data were spatially smoothed with a Gaussian filter (Full width at half maximum (FWHM) 8 × 8 × 8 mm), and spatially normalized. The cerebral activation was rendered either onto T1 brain slices or on the surface of a standard MNI brain. The box-car designed the task that was used and convolved with a hemodynamic response function.

T statistics were calculated for each voxel and \( P < 0.001 \) was considered to be a statistically significant threshold for significantly activated areas that were correlated for multiple comparisons. The maximal BOLD signal changes were calculated for each subject in the motor area M1 before and after HD sessions. Activation maps were calculated and overlaid on the anatomical images. Group analysis of the data was performed, 3D rendering maps were calculated, and the average volume and the maximum intensity of BOLD signal in the activated area M1 was determined for all studied patients before and after the HD sessions.

The ethics committee of the ‘Hospital-University Ethics Committee of Fez’ approved our study in the various centers involved, and we have provided a statement of Ethical Approval from the Hospital-University Ethics Committee of Fez, Morocco.

RESULTS

Visual evaluation

Functional BOLD-fMRI maps were obtained from the HD patient before and after HD session; the individual maps are shown in Fig. 1. Although the individual maps were originated from different individual patients, they cover the same anatomic area in each case, and this is valid for maps obtained before and after HD sessions. The visual evaluation of the images of patient’s maps showed an activated brain in the motor area M1. Qualitatively, the strength of the activated cortical area is stronger before the HD versus after HD sessions. In addition, the activated volumes of the motor area were shown to be elevated after the HD session versus before the HD (Fig. 2). This representation provides a global view of the brain, while displaying activations that have already been observed in a 2D image in sagittal, coronal, and axial. Results of group analysis before and after HD sessions are reported in Figs. 3 and 4; these figures correspond to 2D and 3D representations respectively. Indeed, whole brain analysis comparing cerebral activation between the two major conditions with respect to baseline/random navigation revealed an important visual decrease in the intensity of brain activation of the motor area after HD, and an important visual increase of the size of the volume of brain activation.

Semi-quantitative evaluation

The semi-quantitative BOLD-fMRI results were obtained for cortical brain activity before and after HD. These results were correlated to the OS while reflecting brain activation and functional control reorganization before and after the HD session; this might reflect HD brain plasticity induced. In addition, semi-quantitative biological parameters reflecting the level of the OS were also reported while reflecting HD inducing OS.

We have presented the individual results classified into two groups in order to have the first five patients with the shortest HD duration (from P1 to P5) and the second with the longest HD duration (from P6 to P9), to show the influence of the duration of the HD process on the results.

Semi-quantitative BOLD-fMRI study results

The maximum BOLD-fMRI signal in the individual activated brain areas has shown a systematic decrease in all studied patients after the HD sessions (Fig. 5A) with a small difference between the two groups classified according to the length of the duration of HD; this reflects a decrease of the strength of very localized hemodynamic response and expresses a very localized decrease of the metabolic involvement in the brain functional activity of the involved motor area M1. In contrast, a systematic increase of the volume of the activated brain area involved in the brain function control was recorded in all studied patients after
Fig. 1. Individual activation maps of two patients in the motor cortex M1 overlaid on anatomical images obtained before (A) and after (B) the hemodialysis sessions.

Fig. 2. Individual 3D rendering on a standard brain showing activation of two patients in the motor cortex M1 and projections in the stereotactic Talairach space obtained before (first column) and after (second column) the hemodialysis sessions.
the HD sessions (Fig. 5B) with a significant difference between the two groups classified according to the length of the duration of HD; this reflects a localized expanding hemodynamic response expressing an enlargement of localized increase of the metabolic involvement revealing an increased involvement of additional brain tissue in the brain functional activity involving the motor area M1. The group analysis results confirmed the individual analysis tendency for both maximal BOLD signal and BOLD signal volume after the HD session (Fig. 5C, D) in all averaged patients. Additionally, the Analysis of Variance (ANOVA) tests were performed to find out the significance of the difference between groups of maximal BOLD-fMRI signal before and after the HD sessions and found a significant difference between maximal BOLD-fMRI groups with a P-value of 0.05. Similar ANOVA test was achieved to find the significance of the difference between groups of volume of the activated brain area before and after the HD sessions and found a significant difference between volumes of the activated brain with a P-value threshold of 0.05.

Semi-quantitative biological study results

The MDA marker of OS of the individual patients before and after the HD sessions demonstrated a clear and
systematic increase of the OS after the HD sessions (Fig. 6) with a significant difference between the two groups classified according to the length of the duration of HD. The statistical analysis of the MDA groups before and after the HD sessions using ANOVA found a significant difference with a \( P \)-value less than 0.03. In addition, the TAOA measured in the individual patients before and after the HD sessions demonstrated a clear and systematic decrease of the total anti-oxidant activity after the HD session (Fig. 7) with a significant difference between the two groups classified according to the length of the duration of HD. The statistical analysis of the TAOA groups before and after the HD sessions using ANOVA found a significant difference with a \( P \)-value less than 0.003.

**Semi-quantitative correlation of BOLD-fMRI and biological studies results**

The correlation of the BOLD-fMRI maximal signal intensity and also the volume of the activated cortical brain area behaviors to the MDA behavior found correlation coefficients of 0.92 and 0.98 respectively. In addition, the correlation of the BOLD-fMRI maximal signal intensity and also the volume of the activated cortical brain area behaviors to the TAOA behavior found correlation coefficients 0.912675 and 0.975343 respectively. These results confirmed the strong relationship existing between increased OS and decreased total anti-oxidant activity on one hand and both the maximal BOLD-fMRI signal intensity and the volume of the activated cortical brain area on the other hand.

**DISCUSSION**

The current study was designed to investigate whether fMRI with a motor task is a sensitive method to detect changes in BOLD response occurring before and after HD, and demonstrate that HD has an impact on OS as well as on brain function that can be measured with fMRI as a change in BOLD response in the primary motor area.

This discussion will begin with a brief illustration of the OS process and its involvement in the brain tissue as an introduction to the more general phenomenon of brain plasticity.

**The OS process**

The OS is a physiopathological mechanism occurring in broken oxidation–reduction (REDOX) homeostatic mechanism (Libetta et al., 2011).

This imbalance leads to oxidative damage of various cellular components, which originates the cellular death. Indeed oxygen is an essential element for cells to obtain the energy needed; it is kinetically stable since it has bi-radical conformation, except in the presence of appropriate catalysts which blur the electron spins states to produce the ROS which have more important reactivity compared to oxygen with very unstable and toxic properties (Zauner et al., 2002; Albert et al., 2003).

ROS are derived from oxygen metabolism and are present in all aerobic entities (Agarwal and Prabakaran, 2005) and are vital for life in reasonable doses since they ensure various physiological functions during growth or in defending the body (Favier, 2003; Barouki, 2006). These radicals are very reactive especially the hydroxyl radical (\( ^{•}\text{OH} \)), and are responsible for the mutagenic and toxic effects of oxygen (Gandhi and Abramov, 2012). The figure below demonstrates the tract of evolvement and production of various FRs (Haddad, 2004; Gandhi and Abramov, 2012) (Fig. 8).

**The OS in the brain tissue**

The brain is involved in very high metabolism compared to other tissues, and depends almost exclusively on the oxidative phosphorylation allowing the production of energy. The smooth operational running of brain neurons depends on a rich and continuous supply of oxygen.
Active neurons consume huge oxygen quantities, while producing high rates of ROS; hence the brain is highly exposed to the OS (Massaad and Klann, 2011). The neuronal functions such as axonal transport and synaptic transmission require huge quantities of energy produced by oxidative phosphorylation. Hence, any disorder in the energy metabolism might stimulate the OS and neuronal death (Chauhan and Chauhan, 2006; Huang et al., 2012). Besides, the brain tissue encloses a large number of polyunsaturated fatty acids leading to more ROS, lipid peroxidation and subsequently OS in the case of brain damages.

The OS in neurodegenerative disorders
Many papers demonstrated the implication of the OS in the neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson (PD) Mandel et al. (2003); Von Arnim et al. (2010), these studies highlighted high rates of lipid peroxidation markers (MDA and 4-hydroxynonenal) in the brain of patients (Lovell et al., 1995; Dalfo et al., 2005).

The OS in brain development and plasticity
The immature brain is particularly vulnerable to FRs. This organ highly exhibits the OS (Ravagnan et al., 2002; Blomgren et al., 2007; Ikonomidou and Kaindl, 2011). Studies have shown the implication of the ROS during the brain development in terms of signalization molecules and in the modulation of synaptic plasticity (Serrano and Klann, 2004; de Magalhaes, 2005). Indeed the disappearance of the neuronal mass might originate the organization of the brain function control by surviving brain neurons which yields a brain plastic change accompanying the OS phenomena (Mandel et al., 2003;

The OS in HD patients

The OS is highly prevalent in HD patients because of several factors such as malnutrition which decreases the absorption of food antioxidants (Ha et al., 1996; Jahromi et al., 2010). Besides, a clear reduction of antioxidants is noticed in the HD process (Hu et al., 1993; Ha et al., 1996; Coombes and Fassett, 2012). The limited biocompatibility of the HD membrane also contributes to an increase in the production of the ROS in HD patients (Horl, 2002; Morena et al., 2002; Libetta et al., 2011; Takemoto et al., 2011). Furthermore, the bacterial accumulation in the dialysate while crossing the HD membrane stimulates the discharge of the ROS by polynucleotide neutrophils (Amore and Coppo, 2002; Horl, 2002). It is to consider that the renal failure itself contributes intensely to the OS phenomenon (Siems et al., 2002; Oberg et al., 2004; Libetta et al., 2011; Coombes and Fassett, 2012).

The brain plasticity originated by OS in HD patients

Indeed strong evidences were shown to correlate OS phenomenon and HD (Boaz et al., 2000; Descamps-Latscha and Witko-Sarsat, 2003; Steghens et al., 2005). This study showed a significant increase in lipid peroxidation markers particularly MDA, and a decrease in serum antioxidants.

Considering the direct OS behavior in the brain tissue yielded by the higher brain oxidative metabolism and the lower antioxidant enzyme activity levels in the brain compared to the kidney and the liver, the low bioavailability of antioxidants in the blood resulting from HD is worsening the OS in the brain tissue (Weinstein et al., 2000; Wratten et al., 2000).

So far, the assessment of the OS is done using biological and biochemistry parameters, indeed these parameters allow quantifying the average OS in the human blood. Hence, introducing the BOLD-fMRI which is a known imaging approach allows the space localization of the brain oxygenation change (Tamura et al., 2002; Zhang et al., 2011). This technique is sensitive to local oxygen change in the brain vasculature affected by neuronal tissue demand following neuronal activity ensuring functional control (Kim et al., 2004; Christen et al., 2012).

In this study, it was seen that very localized changes of brain oxygenation while achieving identical functional activity were systematically demonstrated in all studied patients.

This methodology, based on a new aspect, and used for the first time in HD showed a total concordance with the serological results; indeed we found a significant decrease in the intensity of brain activation of the motor area M1 after HD, which is inversely correlated with levels of OS. This correlation is demonstrated by other studies that have assessed the OS in renal failure by the technique of BOLD-fMRI but was primarily a detection of intrarenal oxygenation and not cerebral (Evans et al., 2008; Thoeny et al., 2008; Chandarana and Lee, 2009).

Consequently, the BOLD-fMRI brain is able to provide reliable results compared to the conventional method which is generally based on the TBARS technique estimating lipid peroxidation. Our BOLD-fMRI results demonstrated a high sensitivity to the oxygenation level and OS in HD patients before and after the HD processing using the Polysulfone membrane.

Especially, it is known that BOLD-fMRI has provided new insights into brain plasticity with a valuable method for non-invasive in vivo evaluation of longitudinal changes in brain cortical activation.

The BOLD-fMRI quantifications were expressed in terms of major BOLD imaging quantities. First, the volume of the activated area in the brain during the functional control that is expressing the volume of the hyper oxygenated area. Second, the maximal intensity of activation of the activated cortical area that is reflecting the highest density of the oxygenation of this cortical area following the execution of a given functional task; and in the light of the above, these two quantities demonstrated a systematic change in all investigated patients witnessing brain plastic changes induced by the HD process hence by a change in the OS and oxygen availability in localized tissues of the brain (Habas, 2002). We do support that the blood oxygenation was systematically changed in the whole body of HD patients and was possible to demonstrate in the brain, through the motor paradigm used.

Indeed, it is well established that the neuronal tissue is particularly sensitive to OS (Chauhan and Chauhan, 2006; Massaad and Klann, 2011; Huang et al., 2012). These factors might induce neuronal death and might intermittently decrease the activation potential of neurons, hence decrease the much localized demand on oxygenation which in its turn decreases the perfusion and blood volume supply. These phenomena were reflected by decreased maximal BOLD intensity in the activated corti-
cal brain area after HD inducing significant OS. In contrast, the requirement of the control of the identical functional activity induced an activation of a significantly larger volume area with significantly decreased intensity reflected by a significant decrease of maximal BOLD-signal and increased volume.

These phenomena expressed a balance of cortical activation between two duals (higher maximal BOLD signal, smaller activated volume) to (lower maximal BOLD signal, larger activated volume) before and after the HD session respectively. This duality might underline a duality in the organization of the cortical control of motor function originated by the change in the OS after those patients underwent the HD process. Fig. 9 illustrates the plasticity underlying and accompanying the HD process.

Brain plasticity may occur with neural function following neighboring regions that optimally support the task-related neural activity. Results showed that HD induced two types of changes in BOLD response: BOLD max signal intensity decreased while the area of significant BOLD response increased in the primary motor cortex after HD. These changes were significantly correlated with increased markers of OS.

Indeed, earlier reported studies of HD effects, seems to demonstrate a change of the functional capabilities of patients (Pickett et al., 1999). However, it is difficult to explain why OS in HD patients will influence brain plasticity because we cannot isolate the specific effect of HD considering that other factors occurring in HD patients might impact the plasticity such as accelerated aging that was well demonstrated in this category of patients (Dalfo et al., 2005), and also there are many limitations of the study, the major one is the recruitment of a small number of chronic renal failure patients, in addition, all our subjects were male which limits the generalization of our findings to female patients.

Also, the results showed that the duration of the HD process has an influence on the results which is manifested by the amplification of the OS in the group of patients with the longest HD duration which is in agreement with previous studies (Valentini et al., 2008) which had an impact on the two types of changes in BOLD response as they were significantly correlated with increased markers of OS.

CONCLUSION

The OS is systematically increased in HD patients after the HD process. Indeed, the BOLD-fMRI shows a remarkable sensitivity to brain plasticity and reorganization of the functional control of the studied cortical area. Our results confirm the superiority of the BOLD-fMRI quantities compared to the biological method used for assessing the OS while not being specific, especially in the motor cortex studied, for following the evolution of the OS in HD patients’ brain. They show a systematic and consistent change in all patients’ brain tissue reflecting that increased OS accompanies the standard HD procedure. BOLD-fMRI is expected to be a suitable tool for evaluating the plasticity process evolution in HD brain patients.

Finally, various strategies must be designed for evaluating the progression of the brain plasticity and impairment of cognitive and motor-sensory functional control in HD patients and more research will be needed with greater knowledge regarding these phenomena.

AUTHORS’ CONTRIBUTIONS

RB: First draft writing, study analysis; SB: Study design, writing, study analysis, reviewing; AH: technical support and supply; MM: Patient’s management and reviewing; RM: PhD supervisor of RB; FB: patients management; TS: Early study design and patient’s management; ME: Early study design, reviewing; ST: Patient’s management, technical and logistic support.

CONFLICT OF INTEREST

The co-author ME claims the right of the last position in the authors list without being supported by any of other authors.

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