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EC CLINICAL AND EXPERIMENTAL ANATOMY
Research Article

Apathy and Depression in People Living with HIV: Differential Attentional and Functional Neuroimaging Alterations

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Received: July 01, 2019; **Published:** October 25, 2019

Abstract

People living with HIV (PLHIV) have a high prevalence of depression and apathy that negatively impact daily functioning, are associated with neurocognitive disorders and have resistance to psychopharmacological treatment. The objective was to determine the prevalence of depressive disorder and apathy in PLHIV, to describe its impact on attention and on functional neuroimaging, with specification of the differential parameters applied to the care clinic. We studied 38 male PVVIH with negative viral load, neuropsychiatric, neuropsychological evaluations were applied and images were taken with Single Photon Emission Tomography. We observed that apathy significantly altered the previous attentional network with a characteristic pattern. We found hypoperfusion in the anterior cingulate that was correlated with the perfusion of the striatum and insula, and with the score in the apathy test.

Keywords: *HIV; Depression; Apathy; Attention; Functional Neuroimaging*

Introduction

Since the medical description of the human immunodeficiency virus (HIV) infection in a CDC report of only 553 words, dated 6/5/1981, the international community attended one of the diseases with the greatest impact on research (biomedical as clinical) as well as in the legal, bioethical, social and interpersonal fields of daily life. The CDC undertook a national registry in the US and in this way began 38 years ago the coexistence of society with a virus that generated unprecedented changes, it isn´t compared with other infectious diseases because of the rapidity in time and depth in different areas as analogues (Sontag, 2012; Zyrulnik, 2000).

From the strictly biomedical skill, there are multiple publications on virology and antiretrovirals advances. There are more than 20 antiretroviral drugs that combined generate multiple regimens or treatment schemes for different stages of disease progression. There are also many advances regarding the comorbid pathologies of HIV and its therapeutic approach (American Psychiatric Association, 2000; Barclay., *et al.* 2007), but in the topic of mental health and cognitive neuroscience applied to the PLHIV´s clinic the advances have been significantly lower compared to the others skills. There is limited information on the development of the pathogenesis and clinical typologies of neurocognitive disruption in PLHIV, its neuropsychological evaluation and therapeutic approach methodologies, although there are many reports and research in the literature on dementia.

Depressive symptoms have high prevalence and importance in chronic diseases and can be a limitation and complication due to their negative impact. People living with HIV (PLHIV) present clinical specificities in their depression with an important prevalence of apathy and resistance to treatment, which generates underdiagnosis, inconclusive treatment, greater suicidality and association with neurocognitive alterations.

Objective of the Study

To determine the prevalence of depressive disorder and apathy in PLHIV, to describe its impact on attention and functional neuroimaging, with specification of the differential parameters applied to the care clinic.

Materials and Methods

The study group consisted of 38 PLVIH, negativized viral load, male sex, age between 26 and 49 years (average = 37.49, DS = 7.4), all of them receiving the corresponding HAART (high anti-retroviral activity therapy), with diagnosis of depressive disorder (F32.9, DSM IV) and signs of apathy. The exclusion criteria were: neurocognitive impairment, psychopharmacological therapies use (antidepressant, antipsychotic or antiepileptic), central neurological therapies, other mental or behavior disorders, addictive substances use, autoimmune or systemic diseases other coinfections (HCV), hematological or central vascular illnesses, head trauma or neurosurgeries. All participants received a neuropsychological and neuropsychopsyquiatric evaluation through the MINI International Neuropsychiatric Interview, 2 scales for depressive disorder valuation (PHQ-9 and Hamilton Depression Rating Scale- HDRS-) and an apathy scale (Apathy's Valuation Scale clinical version) AES-C " [1]) and neurocognitive tests (Stroop test, Trail Making Test A and B, Digito symbol, d^2 test). All participant´s brains were studied using functional neuroimaging (SPECT 99Tc- ECD) (Figure 1) with mitigation correction (Chang´s method) [2] and semi-quantitative analysis (Tanaka., *et al.* method). Statistical parameters were applied and ethical-legal norms were accomplished (Good Clinical Practice, ANMAT Disposition 6677/10 and adhesion to the Ethic Principles with origin in Helsinsk´s Declaration).

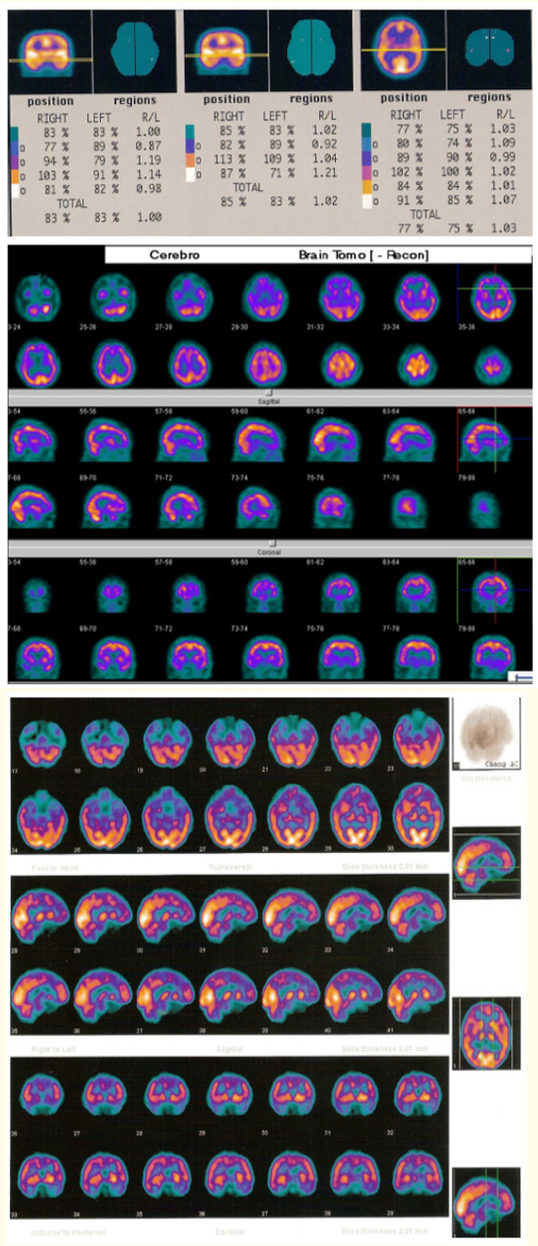
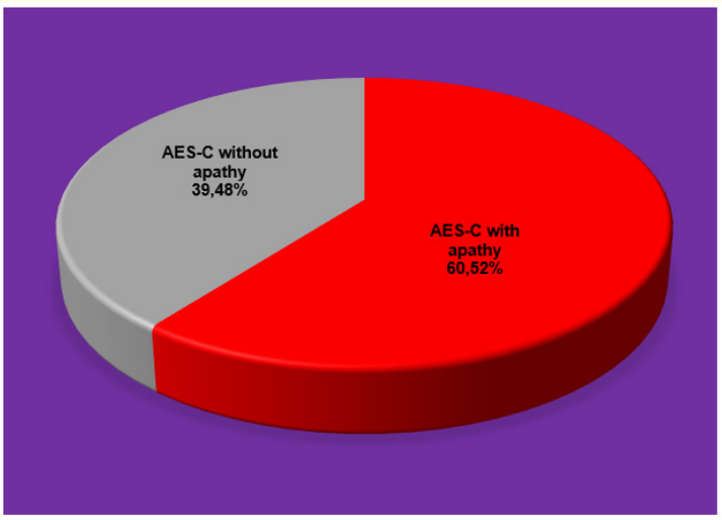


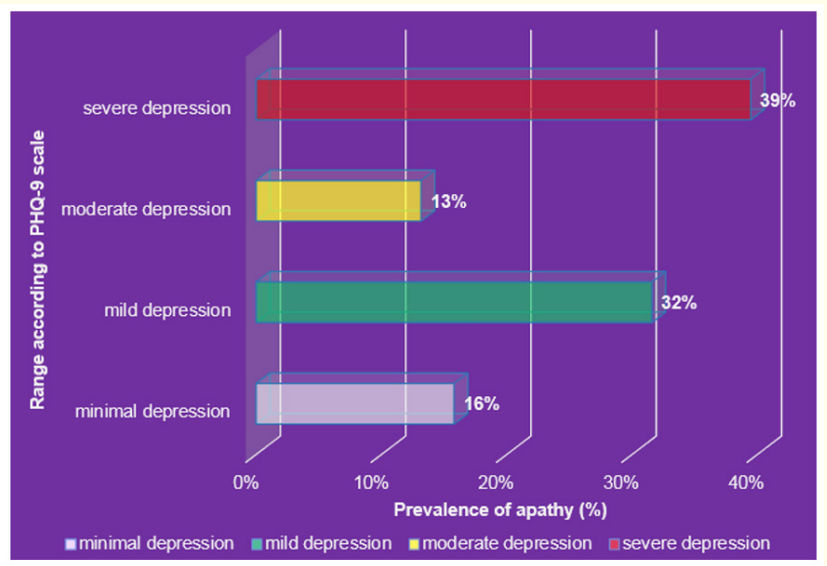
Figure 1: *Images from SPECT in PLHIV with apathy, semi-quantitative analysis.*

Results

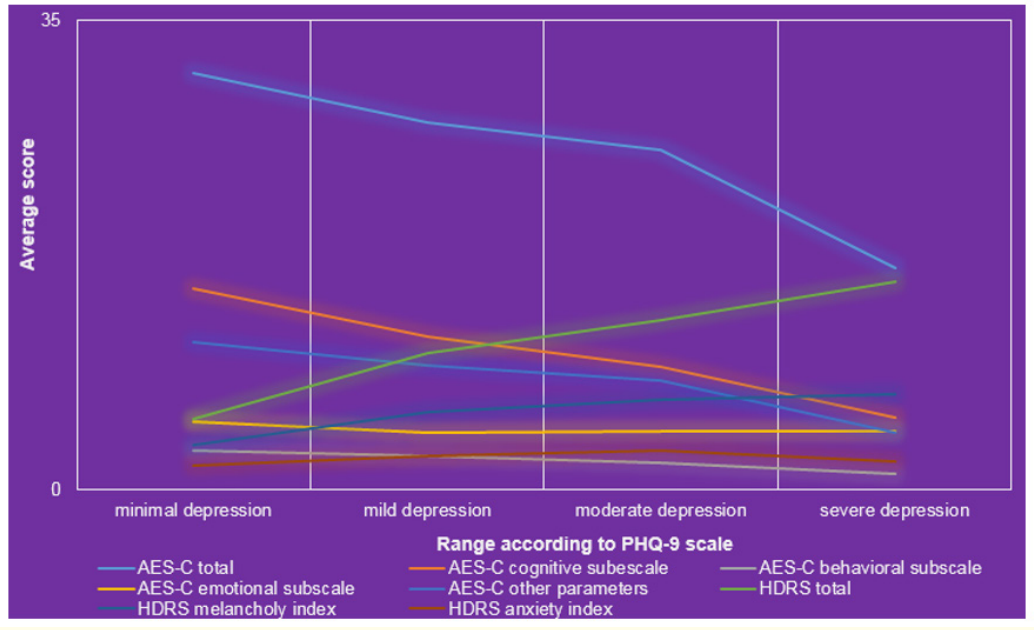
We found that 60.47% of PLHIV with depressive disorder had results in the apathy range according to the AES-C scale (Graph 1). We object to an increase in cases with apathy according to severity in the PHQ-9 scale (Graph 2). The severity in PHQ-9 was proportional to the prevalence and alteration in the AES-C in the cases with apathy and the total HDRS score and its melancholy index, but inversely proportional to the total score and of the cognitive and behavioral subscales in AES -C (Graph 3). PLHIV with apathy had a higher prevalence of cases with moderate depression according to HDRS (Graph 4) against those who had no apathy; and higher average score in PHQ-9 ($p < 0.01$), total HDRS ($p < 0.05$), HDRS melancholy index ($p < 0.01$) and index of sleep disorders ($p < 0.05$) (Graph 5). The greatest alteration in the apathy scale (lowest score) was inversely proportional to the HDRS score ($r^2 = 0.78$), in PHQ-9 ($r^2 = 0.74$) and HDRS melancholy index ($r^2 = 0.71$) (Graph 6).



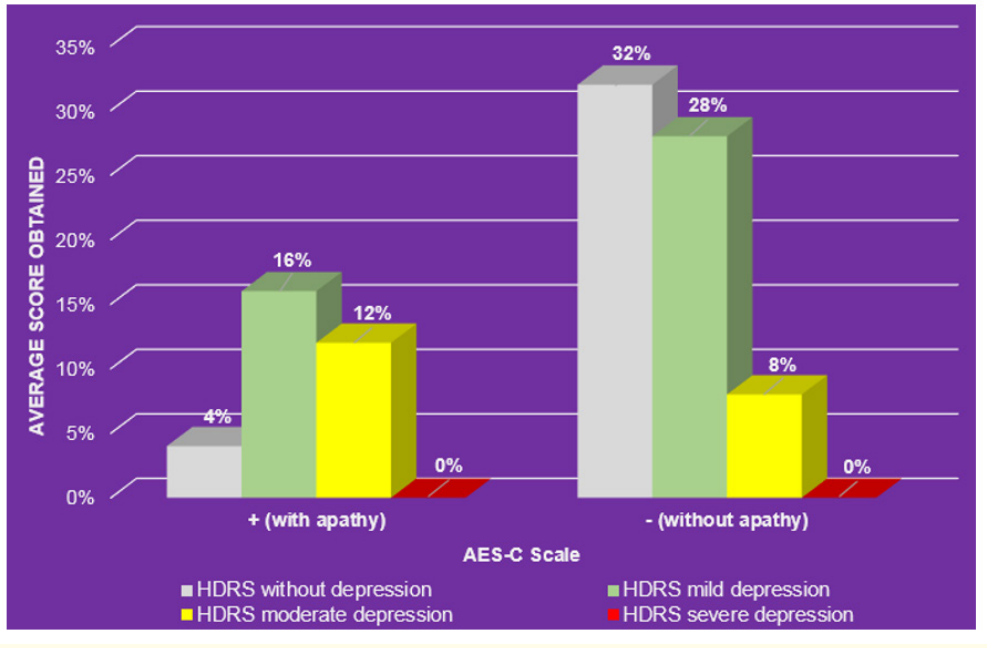
Graph 1: *Prevalence of PVVIH with depressive disorder and apathy.*



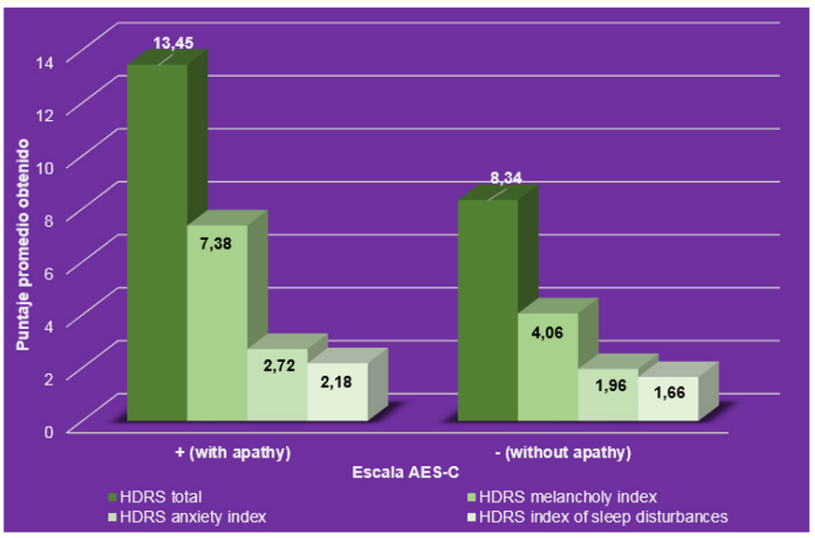
Graph 2: *Prevalence of cases of apathy according to the severity range in the PHQ-9 scale.*



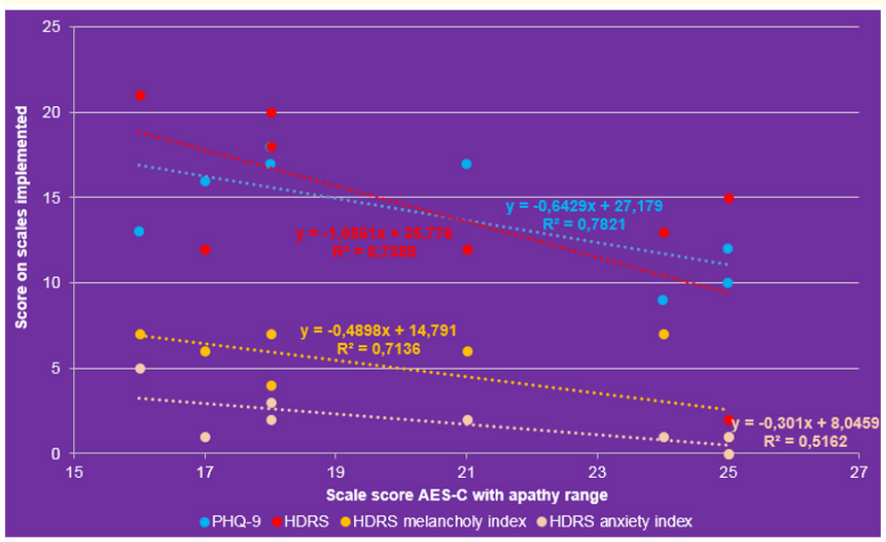
Graph 3: *Results of scales and subscales implemented according to the severity range determined by the PHQ-9.*



Graph 4: *Prevalence of patients and their specification in severity of depression by HDRS Scale according to the existence of apathy determined by Scale AES-C.*



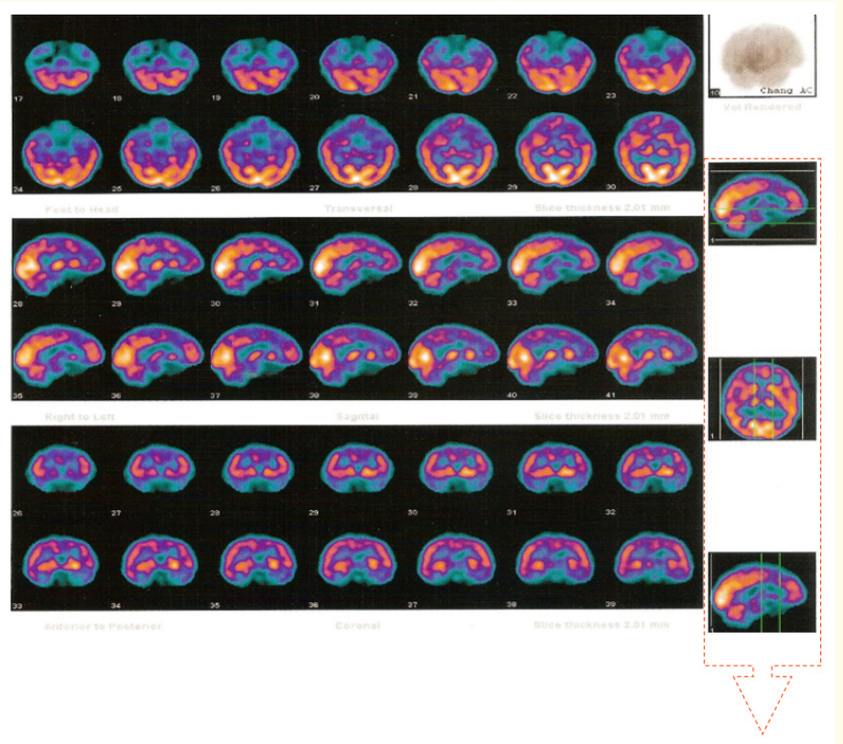
Graph 5: *Average score obtained in indexes (subscales) of the HDRS according to classification between PVVIH with depressive disorder with and without apathy according to the AES-C scale.*

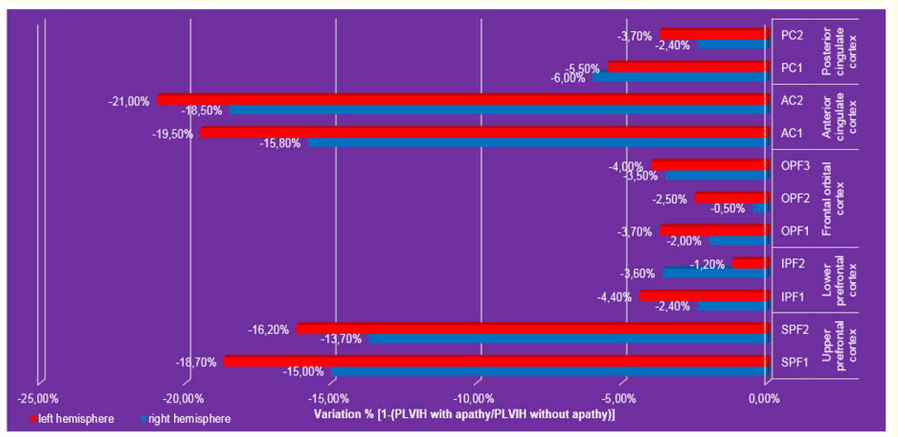


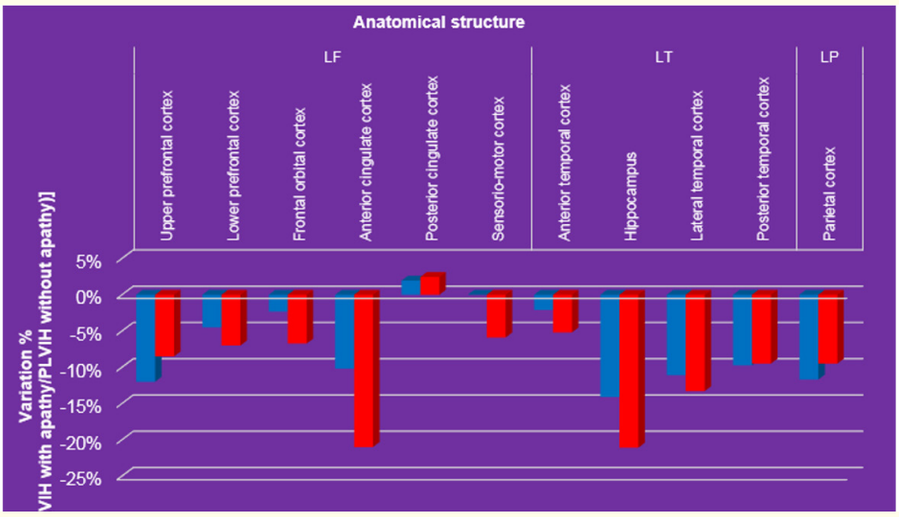
Graph 6: *Correlation between scores in the apathy range according to AES-C and scores in the other scales implemented.*

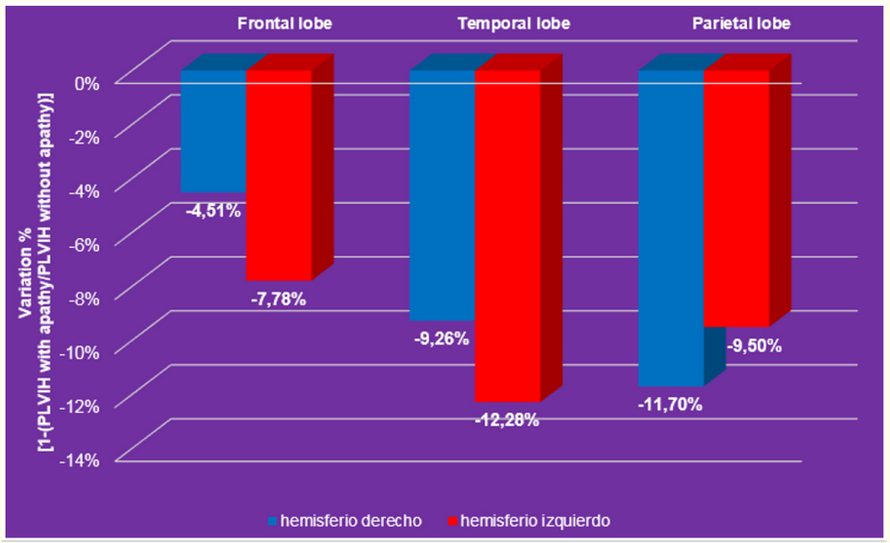
The semi-quantitative analysis applied to neuroimages by SPECT determined absolute hypoperfusion, according to severity in: left former cincture AC1, AC2 (-20.25%), pre-frontal left upper cortex SPF1 and SPF2 (-17.45), left former frontal insula IA and IP (-17.40%), right former cincture cortex AC1 and AC2 (-17.15%), caudate nucleus NC1 and NC2 (-15.80%), left caudate nucleus NC1 and NC2 (-15.35%), with former prevalence, upper pre -front cortex SPF1 and SPF2, right, (-11.20%). When analyzing hypoperfusions by structure, the right caudate nucleus showed more affectation (-15.80%) followed by his contralateral (-15.35%) and left lobe insula (-10.65%) (Graph 7). By correlation graphic we determined in PVVIH with apathy that the perfusion from the left IA insula showed a correlation with the perfusion from left caudate nucleus (NC1: $r^2 = 0.84$) and right (NC2: $r^2 = 0.83$), with the cortex from former left cincture (AC2: $r^2 = 0.77$, AC1: $r^2 = 0.75$) (Graph 8 and 9) and the correlation and implication with the total score in AES-C ($r^2 = 0.80$) and emotional subscale ($r^2 = 0.71$) (Graph

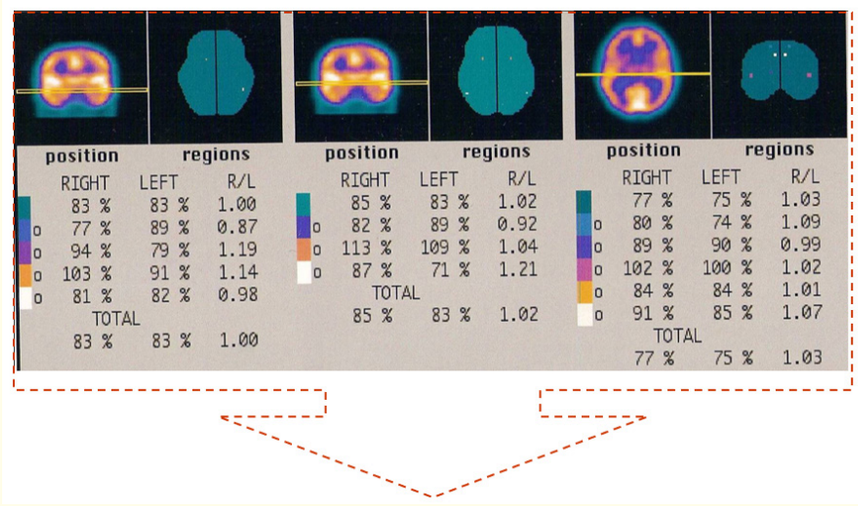
10). Objective through neuropsychological tests that patients with apathy had a significant alteration of alternating and divided attention compared to the focused and sustained (Graph 11).

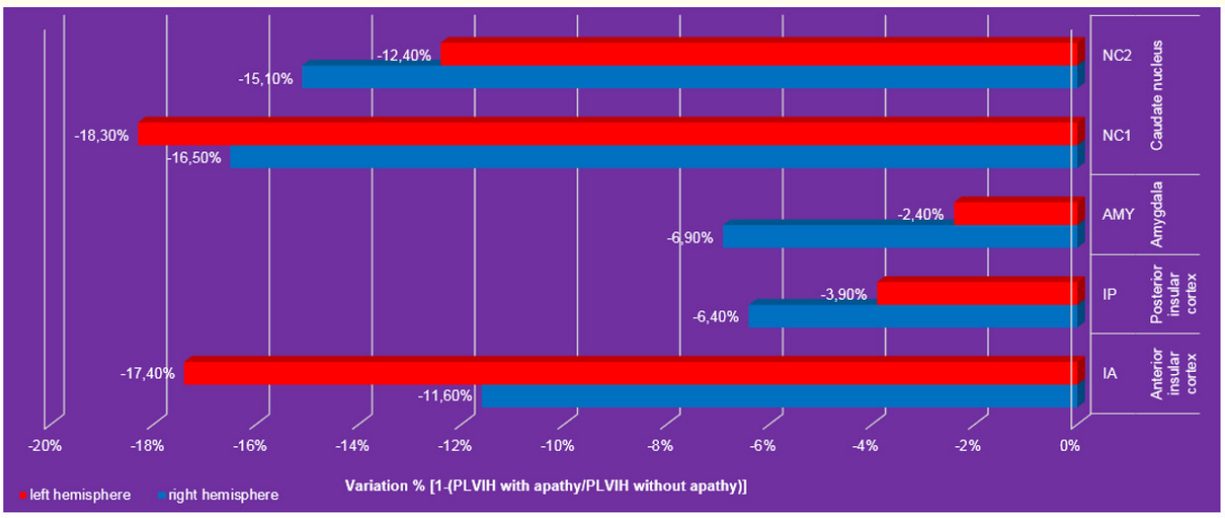




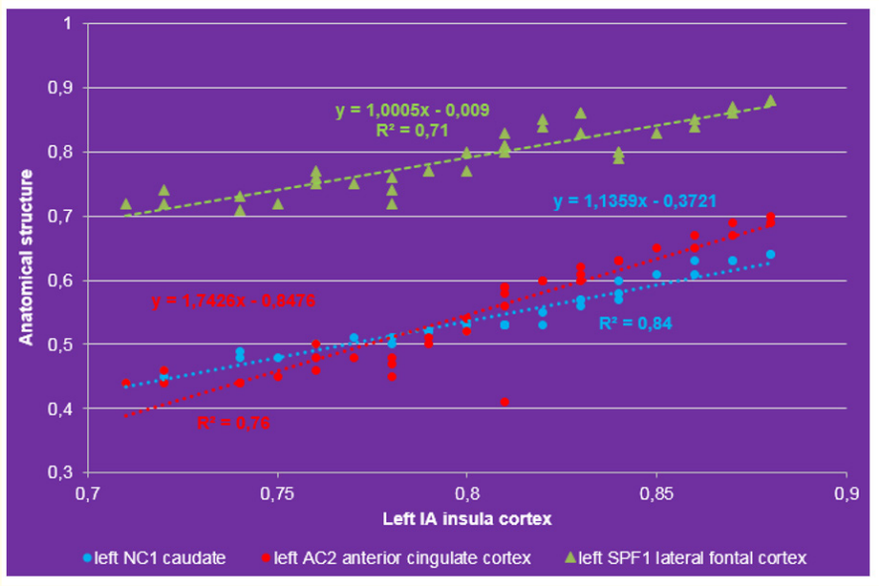




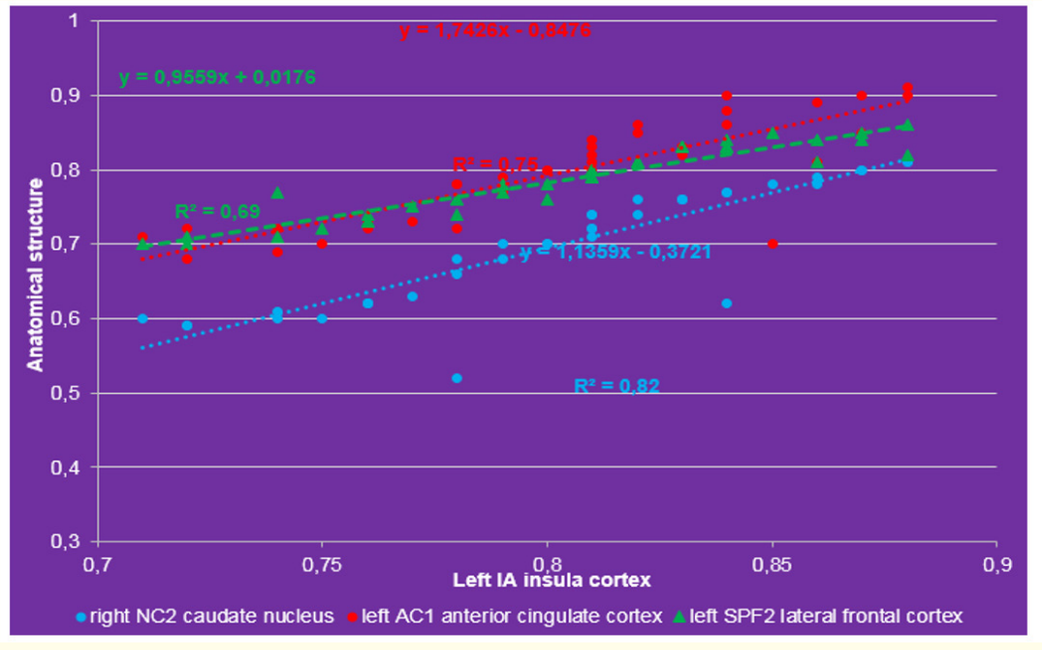




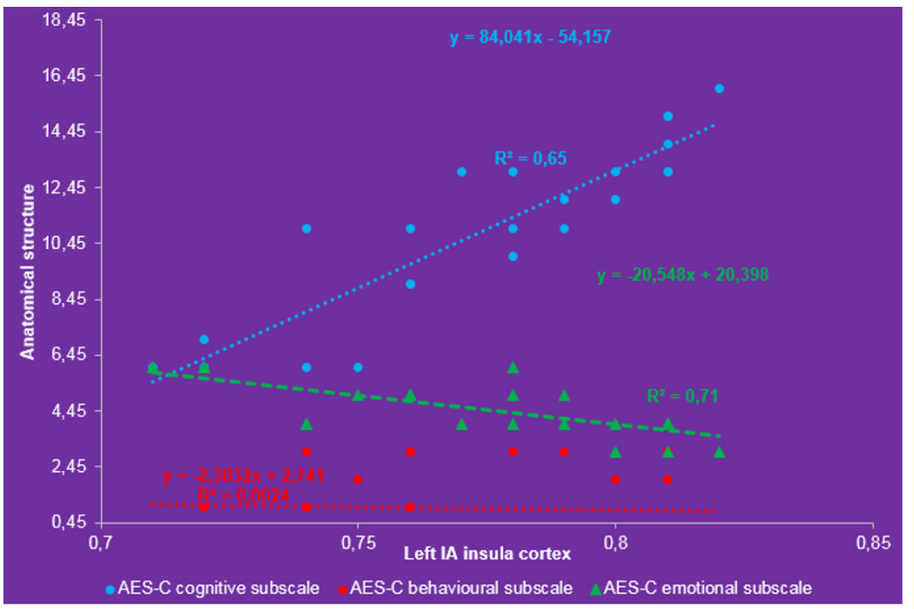
Graph 7: *Correlation between scores in the apathy range according to AES-C and scores in the other scales implemented.*



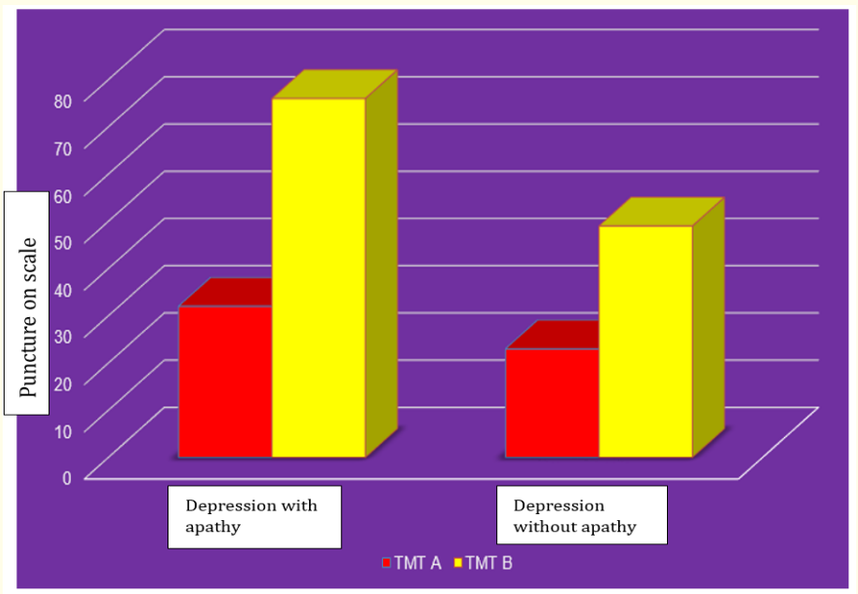
Graph 8: *Correlation between perfusion in the left IA insula and perfusion from caudate NC1, left AC2 anterior cingulate cortex and left lateral frontal cortex SPF1.*



Graph 9: *Correlation from perfusion in the left insula cortex IA with the perfusion in the right caudate NC2, former cincture AC1 and lateral frontal cortex SPF2 in positive HIV patients living with apathy.*



Graph 10: *Correlation between perfusion in cortex from left insula IA with a score in subscale from Apathy´s Scale in patients living with HIV.*



Graph 11: *Result in neuropsychological test applied to assessment of attention circuits.*

Discussion

Depressive symptoms are of multifactorial etiology. These symptoms are an important, limiting and determining complication in chronic diseases due to their negative effect on adherence to treatments, quality of life and the evolution of clinical conditions (Currier., *et al*. 2004). Early detection of psychopathological disorders improves efficacy in the interdisciplinary approach and treatment (Freud-enreich., *et al*. 2010).

The prevalence of depressive disorder in people living with HIV (PLHIV) is greater than the uninfected population and presents clinical-semiological specificities that generate cases of subdiagnosis (for which it is not treated), incorrect or unfinished treatments (due to erroneous choice of medication due to the mechanism of action or interactions with HAART), increased suicidality, mortality due to complications related to AIDS and may be associated or trigger neurocognitive alterations (Baddeley, 1986; Bracy, 1994). The diagnosis of depressive disorder and its therapeutic approach is hindered by the high prevalence of apathy that was reported in PLHIV, both associated with depression and those without depression (Caballero., *et al*. 2005). This situation involves a torpid evolution of mental illness with partial response to SSRI antidepressants given that the neurobiological substrate is not primarily serotonergic; Difficulties for the psychopharmacological approach with current treatment guidelines.

In relation to apathy, which represents the loss of motivation, it is a comorbidity that has interference at different levels, not only emotional, but behavioral and neurocognitive. Although in the continuum of the classifications it was associated or derived from depression, Marin., *et al*. assigned an own nosological entity and Levy., *et al.* on the classification of Stuss., *et al.* [3] describes its 4 subtypes: emotional, cognitive, behavioral and self-activation [1,3]. Different investigations assigned to each subtype a particular neurobiological circuit, which has an association with the receptors and neurotransmitters involved that will be the basis for an effective therapeutic approach. But in all apathy subtypes the point of association and core of the disorder was located in the basal nuclei and their complex bidirectional pathways of interconnection with cortical and subcortical structures [4,5].

The commitment of the dorsomedial-subcortical prefrontal circuit was associated with executive disorders (planning and organization of new objectives); as well as the cingular-subcortical circuit was linked to the motivation and its disorder. Our cases did not show significant involvement of the amygdala but of the caudate nucleus, the cingular-amydala connection being not relevant. The anterior insular cortex connects with thalamus, ventral striatum, amygdala and prefrontal cortex, and is involved in contextual processing for higher order emotions and cognitive. In our research, significant anterior insular commitment was registered, which correlated with the psychopathology of apathy, linking it with the affectation of intrinsic motivation; its altered perfusion was correlative and of greater impact with that of the ipsilateral caudate and provides the severity in the apathy test. This affectation is a differential point for the anatomoclinical correlate.

On the basis of these descriptions in apathy, and the main alteration of the dopaminergic (non-unique) pathways, their comorbidity with depressive symptoms synergistically aggravates the picture put in place not only different structures but different biochemical pathways. It should be noted that, in the primoinfection and then in the evolution of the infection, proteins and particles of the HIV capsid were found in the basal nuclei through immunohistopathological investigations, for this reason it has been postulated that it has an important role in the neurocognitive disruption that It occurs slowly in PLHIV [6-8].

As described above, depressive symptoms and their comorbidity with apathy generate neurocognitive alterations that affect the activities of PLHIV in a heterogeneous manner (Gorman., *et al*. 2009). Different authors investigated separately the impact of depression (Castellón., *et al.* 2000, 2006) and apathy [9] in PLHIV and in few cohorts the coexistence of both tables (Bryant., *et al.* 2015; Castellón., *et al.* 1998; Kamat., *et al.* 2015). In such reports as in those related to HIV-associated dementia, they agree that the attention domain is one of the first to be affected, especially prior to the hippocampus-dependent mnesic circuits [10-18].

Conclusion

Apathy in patients living with HIV with depression presents specific neurocognitive alterations and differentials in the attention domain. Neurofunctional alterations were found in the striatum and the insula, correlated with the involvement of the cingulate cortex.

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Volume 2 Issue 9 November 2019