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Ventro-striatal/Nucleus accumbens alterations in adult ADHD: Effects of pharmacological treatment

A Neuroimaging Region of Interest Study

Mónica Franco Emch
Supervisor: Òscar Vilarroya (UAB)
Tutor: Olga Valverde (UPF)
Universitat Pompeu Fabra

Abstract

The Attention-Deficit/Hyperactivity Disorder (ADHD) is a neuropsychological disorder characterized by inattention, impulsivity and/or hyperactivity. It is one of the most common disorders in childhood with an average prevalence of 5%. Symptoms persist into adulthood in 30-60% of the cases, with 3.4% of the adults maintaining a full-diagnose. Although it is a highly diagnosed disorder, its etiology is still unclear. Currently, the most widely accepted theory points to a dysfunction of the dopamine neurotransmission. ADHD patients present an alteration of the nucleus accumbens (NA). Therefore, this neurostructure is the key target of the pharmacological treatment, mainly Methylphenidate (MPH), which blocks dopamine active transporter (DAT) leading to an increase in dopamine. Despite being the most commonly used pharmacological treatment for ADHD, the neurobiological long-term effects of MPH are poorly understood. Moreover, there is a lack of neuroimaging studies addressing possible changes in brain structure due to pharmacological treatment, especially in adult populations.

Therefore, the aim of this study was to apply a ROI analysis to structural magnetic resonance imaging scans to examine whether there were volumetric differences in the nucleus accumbens (NA). The study compared a group of ADHD subjects (*n=34*) with a group of control subjects (*n=33*). Addtionally, we studied the NA differences between the sub-group of MPH medicated subjects (*n=7*) with the sub-group of medication-naïve subjects (*n=26*). The ADHD group presented a larger NA compared to control group and medicated patients presented a smaller NA compared to non-medicated patients, but none of these differences were statistically significant. It is important to perform more studies with larger and homogeneous samples in order to draw firm conclusions.

Introduction:

The Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by the triad: inattention, impulsivity and/or hyperactivity [1]. It is one of the most common neurodevelopmental disorders in childhood and adolescence with an estimated worldwide prevalence of 5.3% [2]. Symptoms persist into adulthood in 30-60% of the cases, with around 3% of the adults maintaining a full-diagnose [3] [4].

It has been established that a lower prevalence exists in lower income countries in comparison with rich countries [3], which indicates an infra-estimation in poor countries. However, the significant variability in the prevalence could be explained by methodological procedures [5].

The symptoms adopt different intensities according to the period of life, being the schooling the stage where the symptoms are more evident [6]. Older adults show significant lower levels of ADHD symptoms, which indicates that they decrease with age [7]. It is more frequent in men than in women within general population, with an approximate proportion of 2:1 in children and 1.6:1 in adults [1].

Considering the high prevalence of ADHD in adulthood and the negative consequences of the symptoms on the patient's life, it should be recognized as an important disorder of the brain.

Despite being a highly diagnosed disorder, the etiology is still unclear. There are several theories, but the most widely accepted theory remarks a dysfunction of the dopamine (DA) neurotransmission in ADHD people [8] [9].

In an animal model, Zhuang et al [10] generated hyperdopaminergic mutant mice by reducing the expression of dopamine active transporter (DAT) to 10% in comparison to wild-type levels, and they presented hyperactivity, a symptom of ADHD. It has been postulated that not only DAT is associated with this disorder, but also dopamine receptor genes (DRD4 and DRD5) [11] [12][13].

The noradrenergic and the serotonergic neurotransmission systems have been also studied. A polymorphism (1021 C/T) in the enzyme dopamine-beta hydroxylase (DBH) causes poor activities levels of this enzyme. As a consequence, the synthesis of noradrenaline (NA) is impaired, leading to executive function alterations in this disorder [14]. Moreover, one gene of the serotonergic system is implicated in the ADHD symptomatology. The 44-bp deletion in the promoter region of this gene (5-HTTLPR), which is a serotonin transporter, led to lower serotonin activity [13] [15].

In 2002, Sonuga-Barke, [16] explained this disorder trough the dual-pathway model, which shows that two different psychological/developmental processes existed. On one hand, there was a dysfunction in inhibitory control, which left the patients with difficulties in behavioural monitoring, tasks requiring attentional flexibility and planning and working memory, known as the “cool” executive functions [17]. Specifically, these types of executive functions are regulated by the executive meso-cortical dopamine circuit, including the dorsal striatum, dorsomedial thalamus and dorsolateral prefrontal cortex, presented in the frontal region [18] [19].

The results of functional neuroimaging studies conducted among children with ADHD indicate decreased functional connectivity in the fronto-striatal-cerebellar circuits and fronto-parietal-temporal circuits [20] [21] [22]. Likewise, in adult patients there are deficits in these areas [23] [24]. Two studies described that in adults there is also a decrease in the functional connectivity between the anterior cingulate and posterior cingulate cortex regions in comparison to control and only child ADHD, suggesting that this connection should be considered as a place of dysfunction in ADHD [25] [26].

Several structural neuroimaging studies have been also performed [23] in children, and grey matter deficits in the frontal lobes [24] [27], basal ganglia [28], cerebellum [29] and parietotemporal regions [27] have been discovered. A longitudinal study showed that there is a maturation delay in brain structure [30]. Few structural imaging studies have been published in adult ADHD, but they show similar deficits to those observed in children with ADHD [31] [32]. Moreover, subjects with ADHD showed significantly decreased cortical thickness in the right temporal pole, orbitofrontal cortex, [33] [34] bilateral frontal regions and the right cingulate cortex [35]. These results suggest a neuroanatomical profile of the ADHD that involves alterations of the cortical thickness in regions related to attentional processes.

On the other hand, Sonuga-Barke [16] identified an altered reward mechanism, known as “hot” executive functions, which shows behavioural and motivational inhibition. This motivational pathway is associated to the meso-limbic dopamine pathway, which projects dopaminergic impulses from the ventral tegmental area (VTA) to the nucleus accumbens (NA). The NA is a cell mass ontogenetically related to the caudate-putamen complex. However, the caudate and putamen both receive dopaminergic input from the substantia nigra [36].

Some imaging studies of markers of the dopaminergic function in ADHD have been done. They remarked lower availability of DA receptors (D2/D3) and DAT in NA in drug-naïve ADHD participants in comparison to the control participants [8] [38]. These

alterations in the dopaminergic function have been associated with changes in reward mechanisms in ADHD [37], reflecting a motivation-deficit. At a behavioural level [39] [40], ADHD patients have shown a significant preference for small immediate rewards to larger but delayed ones. This strategy allows them to minimize the experience of delayed results.

These findings are associated with the ventral striatum. A decreased activation in the ventral striatum during reward anticipation and a positive association during reward delivery have been showed in ADHD [37] [41] [42].

In adults and young adults, stimulant medications, such as Methylphenidate hydrochloride (MPH), enhance DA signaling and have been used for decades in treating this disorder [6] [43]. MPH is the first-choice medication used to treat this disorder and it enhances dopaminergic neurotransmission by blocking DAT, which are abundant in the striatum [43] [44] [45] and increase inhibitory GABAergic neurotransmission [46].

A study [47] carried out with 23 adult patients during 7 weeks in Massachussets showed a 78% improvement in ADHD patients after taking this psychostimulant. Another study [48] performed with children and adolescents showed an efficacy reduction (54.4%) of the ADHD symptomatology after taking MPH during 6 weeks. Moreover, after one year of pharmacological treatment in adult ADHD patients [49] [50], they also improved their symptoms, showing that continued medication and higher cumulated doses are effective. The long-term efficacy has also been found in children suffering from ADHD [51]. In a review [52] it is indicated that it is also effective in other domains, such as functional impairment and social dysfunction.

All these results indicate that MPH is effective in children and adults suffering from ADHD, but there are some secondary effects. Loss of appetite is the most frequent secondary effect. Insomnia, tics and depression are infrequent, and headache and stomach ache could be presented at the beginning of the administration [6] [53] [54]. Moreover, in a study performed in Italy with ADHD patients, it was concluded that MPH can lead to a significant decrease in height in children [55].

There are some studies which point out that there is an attenuation of the first inducted-increase DA in striatum after long-term treatment with oral MPH [56] [57]. These results show a neuroplasticity effect of chronic MPH and they suggested that 12 month treatment with oral MPH resulted in upregulation of DAT in striatum.

In addition, two studies explained that there is a reduction in the volume of ventral-striatum of medicated ADHD children and adults [28] [58].

As it has been shown, the neurobiological effects of MPH are poorly understood and there are some controversial results. It is known that MPH increases the levels of extracellular dopamine in the striatum, but there is limited literature on loss of efficacy of stimulant medication in long-term treatment. The pharmacological studies corroborate the previous neuroimaging studies about the key role of ventral striatum in ADHD. Moreover, there is a lack of neuroimaging studies about how MPH affects the ventral striatum of ADHD patients and especially in adults.

The aim of this study is to examine whether there are volumetric differences in the NA of ADHD patients in comparison to control groups. We will also investigate whether MPH could affect the volume of NA in ADHD patients.

This study applies a Region of Interest (ROI) analysis to structural magnetic resonance imaging scans to examine the volumetric differences in NA in the aforementioned conditions. This method has the advantage of high face validity because it is possible to examine the images without normalization but, on the other hand, it is time-consuming and does not allow segmentation between grey and white matter [59].

Methods and Material

Subjects

For this study, 36 ADHD patients between the ages of 18 and 55 were recruited at the Hospital del Mar in Barcelona. However, due to poor quality of the images, three patients were removed. Therefore, the ADHD group ended up with 33 ADHD patients (7 medicated and 26 medication-naïve patients) (see Table 1). A team of psychologists and psychiatrists from Vall d'Hebron Hospital in Barcelona evaluated all patients in order to exclude those with other psychiatric or personality disorders. Patients with substance use disorder of drugs or alcohol in the past or in the present were also excluded from the experiment. Moreover, patients with an IQ within one standard deviation from the mean were included. ADHD diagnosis was based on the Diagnostic and Statistical Manual of Mental Disease, Fourth Edition, Test Revised and additional instruments, such as Conners' Adult ADHD Diagnostic Interview for DSM-IV [60], Wender Utah Rating Scale (WURS) [61], the ADHD Rating Scale [62] and the Conners Adults ADHD Rating Scale (CAARS) [63] were used in order to confirm the diagnosis.

7 ADHD patients were under treatment with MPH during the last three years, and they were controlled by their doctor, who was in contact with the department.

The control group was composed by 34 people between the ages of 18 and 55 (see Table 1), and two people were removed because they were 3 standard deviations away from the mean and thus were considered to be outliers of the sample. Therefore, the final simple was 32 people. The exclusion criteria were (1) current or former presence of ADHD; (2) current or former presence of any of the following psychiatric disorders: major depression, bipolar disorder, schizophrenia or related; (3) IQ lower than 80; (4) presence of an addictive disorder, except nicotine; (5) any medical issues that could interfere in the development of the study; (6) pregnancy or natural lactation; (7) being in a pharmacological treatment for the last six weeks with some drug that acts in the dopaminergic system and (8) contraindications for the magnetic resonance.

	Number	Age (SD)	Gender	Treatment
Control	32	37.656 (8.276)	17 ♂, 15 ♀	NO
TDAH	33	37.636 (9.968)	20 ♂, 13 ♀	7 MPH, 26 no MPH

	Number	Age (SD)	Gender
Non-medicated	26	37.077 (9,976)	17 ♂, 9 ♀
Medicated	7	39.714 (10,436)	3 ♂ 4 ♀

Table 1. Demographic data of 4 groups. Age are expressed by their mean value and SD.

Scans

Magnetic Resonance imaging (MRI) acquisitions were performed at the Hospital del Mar in Barcelona on a Philips Achieva 3T scanner.

Image

Region of interest delimitation were outlined in all brains by a single investigator (M.F.) blind to group status in coronal sections, taking into account also the other two sections. Previously, interrater reliability (two raters: M.F. and B.A.) was established (intraclass correlation coefficient (ICC) > 0,998) by independent blinded measurements of 10 training scans.

The program used for delineation was MRIcroN [http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html] and I followed the criteria from Oscar Vilarroya and Gunduz [36], taking into account the following landmarks (Figure 1): first, the posterior position of the NA was established as the most caudal slice anterior to the anterior commissure; secondly, a line perpendicular to the internal capsule was drawn, which demarcated the NA, starting at the most inferior and external point of the lateral ventricle and the area under this line was measured until it disappeared; third, the anterior limit was the most rostral slice before the apparition of the external capsule, separating the caudate from the putamen and fourth, the inferior and medial boundaries were delimited by the paraolfactory gyrus.

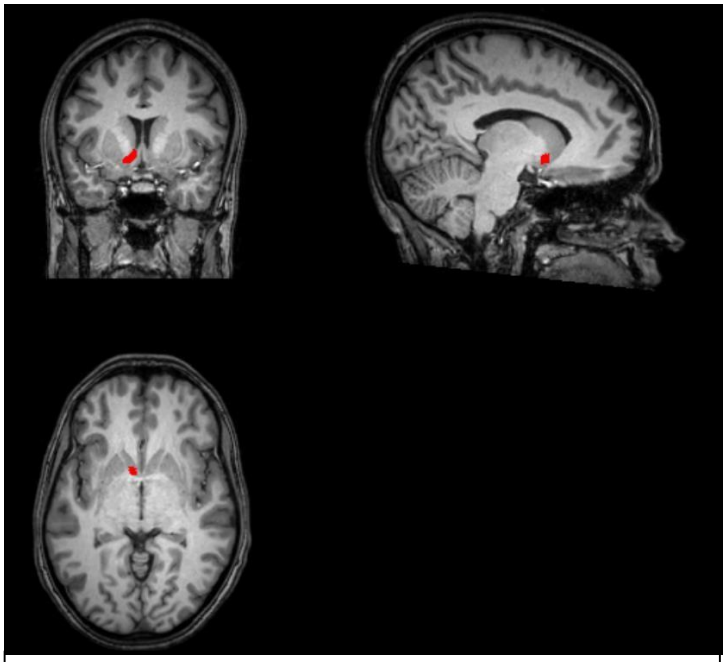

Figure 1. Example of a delimitated NA (ROI)

Statistical analysis

Independent two-sample analysis *t* test were performed with PASW Statistics 18 in order to evaluate the volume of the NA between control and ADHD patients. Moreover, we also performed this test comparing medicated-naïve patients and medicated patients in order to examine whether there were volumetric differences after taking MPH. A general line model was performed in order to examine if gender and/or treatment could affect NA structure.

The NA volume of each subject was divided by the estimated normalized brain volume (NBV), which was extracted automatically with FSLv [64] to not only consider the absolute values of the NA, but also the relative values with respect to NBV.

Results

The *t* tests revealed no significant volumetric differences in NA between ADHD patients and control neither relative values nor absolute values (see Table 2). There was no effect of treatment and/or gender in NA volumes. However, these tests indicated a trend towards an increased NA volume in any condition -right, left and bilateral- in the ADHD group in comparison to the control group (see Figure 2).

	Control Subjects *n= 32* (SD)	ADHD Subjects *n= 33* (SD)	*t*	p	CI 95%	
					Lower	Upper
L. NA	192,956 (47,613)	210,190 (48,442)	-1,446	0,153	-41,043	6,576
R. NA	191,327 (45,491)	205,594 (46,035)	-1,257	0,214	-36,954	8,42
B. NA	384,283 (92,764)	415,783 (93,655)	-1,362	0,178	-77,71	14,709
L. NA /NBV	0,131 (0,033)	0,140 (0,042)	-0,893	0,376	-0,027	0,01
R. NA/NBV	0,130 (0,032)	0,137 (0,040)	-0,714	0,478	-0,024	0,012
B. NA/NBV	0,261 (0,065)	0,283 (0,066)	-1,346	0,183	-0,054	0,011

Table 2. Results of *t* test comparison between control and ADHD subjects in absolute and relative values. The mean value observed in all conditions is calculated in mm^3 and with their correspondent Standard Deviation (SD).

CI: Confidence Interval; NBV: normalized brain volume; L. NA: Absolute volume of left NA; R. NA: Absolute volume of right NA; B. NA: Absolute volume of bilateral NA; L. NA/NBV: Relative volume of left NA; R.NA/NBV: Relative volume of right NA; B. NA/NBV: Relative volume of bilateral NA

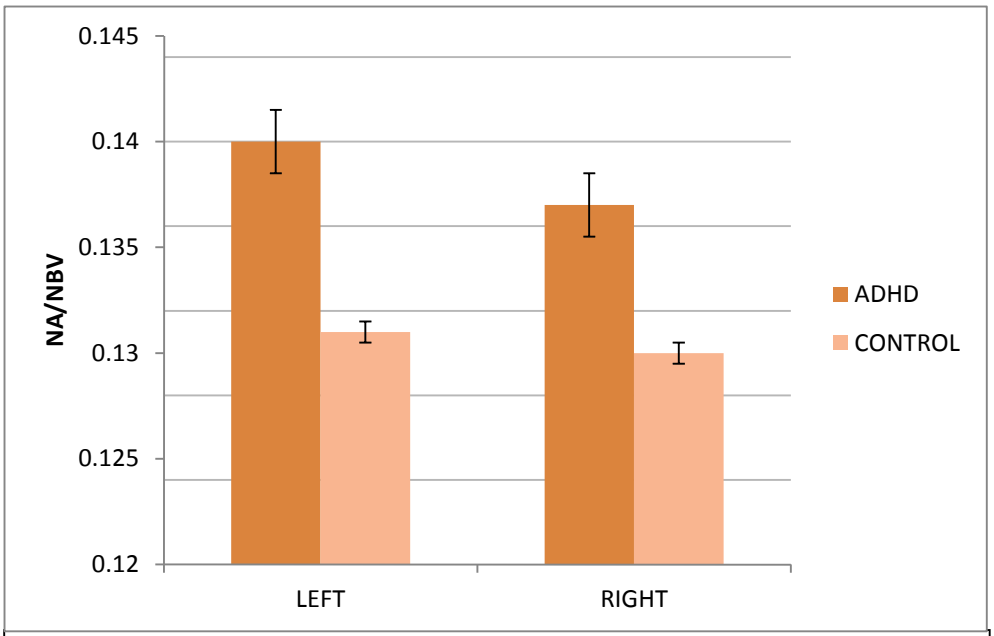

Figure 2. Volumetric differences in right and left NA between ADHD subjects and CONTROL.

NA/ NBV is in mm^3 and represent the relative volume of NA with respect to NBV. Erros bars represent the Standard error of the mean (SEM).

To examine the pharmacological effects of MPH in the ADHD group, we separated this group into two: medication-naïve patients and medicated patients. In this case, the *t* test also revealed no significant differences in the volume of NA between the non-medicated and medicated subjects neither relative values nor absolute values (see Table 3). There was no effect of treatment and/or gender in NA volumes. However, a trend toward reduced NA in medicated patients has been observed (see Figure 3).

	Non-medicated ADHD *n=26* (SD)	Medicated ADHD *n=7* (SD)	*t*	p	CI 95%	
					lower	Upper
L. NA	213,695 (46,525)	197,169 (56,966)	0,499	0,499	-37,079	70,131
R. NA	208,406 (43,509)	195,149 (57,039)	0,572	0,583	-40,234	66,747
B. NA	422,101 (88,964)	392,318 (113,962)	0,641	0,539	-77,203	136,769
L. NA /NBV	0,146 (0,033)	0,133 (0,0382)	0,788	0,452	-0,024	0,048
R. NA/NBV	0,142 (0,031)	0,132 (0,038)	0,657	0,529	-0,026	0,046
B. NA/NBV	0,288 (0,064)	0,265 (0,076)	0,724	0,489	-0,049	0,095

Table 3. Results of *t* test comparison between non medicated ADHD and medicated ADHD in absolute and relative values. The mean value observed in all conditions is calculated in mm^3 and with their correspondent Standard Deviation (SD).

CI: Confidence Interval; NBV: normalized brain volume; L. NA: Absolute volume of left NA; R. NA: Absolute volume of right NA; B. NA: Absolute volume of bilateral NA; L. NA/NBV: Relative volume of left NA; R. NA/NBV: Relative volume of right NA; B. NA/NBV: Relative volume of bilateral NA

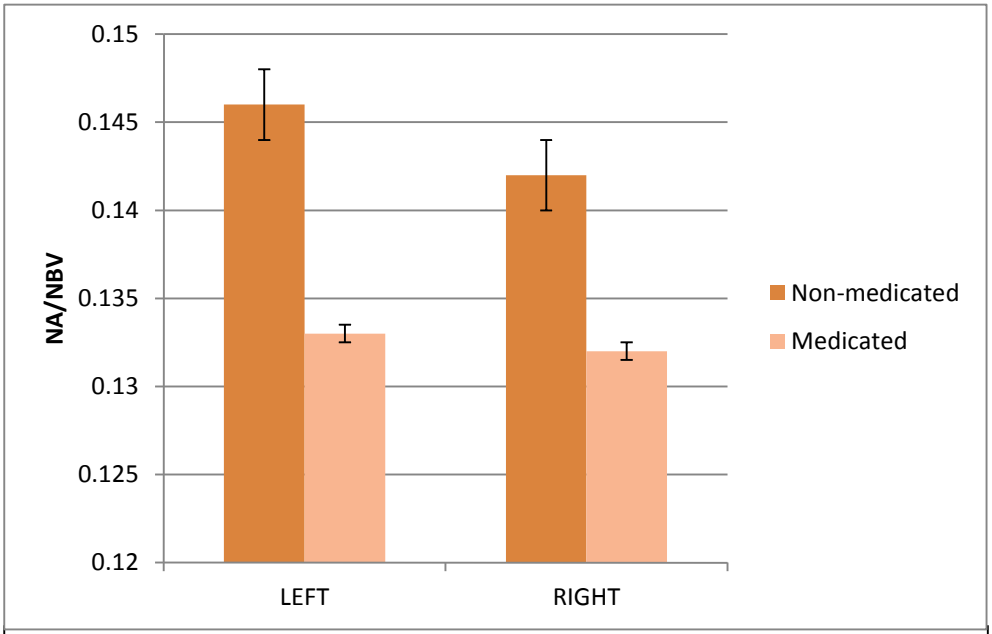

Figure 3. Volumetric differences in right and left NA between non-medicated and medicated ADHD subjects.

NA/ NBV is in mm^3 and represent the relative volume of NA with respect to NBV. Erros bars represent the Standard error of the mean (SEM).

Discussion

The aim of this study was to examine the differences in NA volumes between a group of ADHD subjects and a control group, as well as to examine the NA volumes between an ADHD medication-naïve group and medicated ADHD one, in order to see how psychostimulant medication affects the target of this substance, the NA.

Our results indicate that there are no significant differences between the NA volumes of control subjects and ADHD people. However, we noticed that both left and right NA volumes were bigger in the ADHD. This trend is in concordance with a previous study performed by Seidman et al [32], who observed that the NA is 9.1% larger in adults with ADHD than in control subjects. It could be possible that differences in reward are not enough in order to see neuroanatomical alterations or maybe the differences are too thin. However, in order to draw solid conclusions about the volumetric difference of NA in this disorder, several studies with a larger sample and more homogeneous should be done.

The results also indicated that there are no significant differences between the NA volumes of non- medicated patients and medicated patients. However, we could observe that both right and left NA of medicated patients was slightly smaller in comparison with non-medicated subjects. This trend is in concordance with a study published last year by Hoekzema et al [58]. They observed smaller ventral striatum in adult medicated ADHD subjects in comparison to never-medicated patients. It could be possible that differences between medicated and no medicated are not enough in order to see neuroanatomical alterations or maybe the differences are too thin. However, in order to draw firm conclusions about how MPH affects the volume of NA in ADHD patients in short and long term, several studies with a much larger and homogeneous sample should be done.

It would be suitable to study the differences in NA and other related regions of patients before beginning the medication, during medication and after medication in order to see if changes in ventral striatum are due to MPH exposure or if it is an inherent feature of this neurodevelopmental disorder, as Hoekzema pointed out.

Conclusions

In this study we wanted to investigate the volumetric changes in ventral striatum of adult ADHD patients and also assess whether MPH exposure could modify the volume of ventral striatum of adult ADHD patients. After performing the pertinent experiments, our conclusion is that even though the quantitative analysis showed no significant

differences between the different groups, we could see that ADHD patients (medicated and not medicated) presented a slightly larger NA compared to control group, and that medicated patients showed a reduction of this key neurostructure. Further studies should be performed in order to examine these trends.

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Figure 2. Volumetric differences in right and left NA between control and ADHD subjects.

NA/ NBV is in mm^3 and represent the relative volume of NA with respect to NBV. Erros bars represent the Standard error of the mean (SEM).

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